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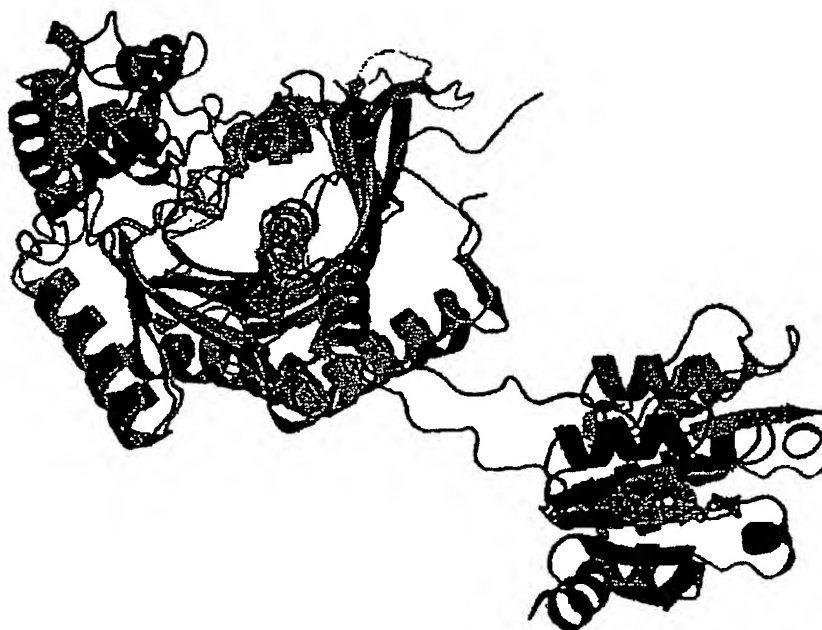
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(54) Title: NOVEL PURIFIED POLYPEPTIDES FROM ENTEROCOCCUS FAECALIS



(57) Abstract: The present invention relates to novel drug targets for pathogenic bacteria. Accordingly, the invention provides purified protein comprising the amino acid sequence set forth in SEQ ID NO: 4. The invention also provides biochemical and biophysical characteristics of the polypeptides of the invention.

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NOVEL PURIFIED POLYPEPTIDES FROM ENTEROCOCCUS FAECALIS**RELATED APPLICATION INFORMATION**

This application claims the benefit of priority to the following U.S. Provisional
5 Patent Applications, all of which applications are hereby incorporated by reference in their
entirety.

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U.S.S.N. 60/400,435	August 1, 2002
U.S.S.N. 60/453,405	March 10, 2003

INTRODUCTION

The discovery of novel antimicrobial agents that work by novel mechanisms is a
10 problem researchers in all fields of drug development face today. The increasing
prevalence of drug-resistant pathogens (bacteria, fungi, parasites, etc.) has led to
significantly higher mortality rates from infectious diseases and currently presents a serious
crisis worldwide. Despite the introduction of second and third generation antimicrobial
drugs, certain pathogens have developed resistance to all currently available drugs.

15 One of the problems contributing to the development of multiple drug resistant
pathogens is the limited number of protein targets for antimicrobial drugs. Many of the
antibiotics currently in use are structurally related or act through common targets or
pathways. Accordingly, adaptive mutation of a single gene may render a pathogenic
species resistant to multiple classes of antimicrobial drugs. Therefore, the rapid discovery
20 of drug targets is urgently needed in order to combat the constantly evolving threat by such
infectious microorganisms.

Recent advances in bacterial and viral genomics research provides an opportunity
for rapid progress in the identification of drug targets. The complete genomic sequences
for a number of microorganisms are available. However, knowledge of the complete
25 genomic sequence is only the first step in a long process toward discovery of a viable drug
target. The genomic sequence must be annotated to identify open reading frames (ORFs),
the essentiality of the protein encoded by the ORF must be determined and the mechanism
of action of the gene product must be determined in order to develop a targeted approach to
drug discovery.

30 There are a variety of computer programs available to annotate genomic sequences.
Genome annotation involves both identification of genes as well assignment of function

thereto based on sequence comparison to homologous proteins with known or predicted functions. However, genome annotation has turned out to be much more of an art than a science. Factors such as splice variants and sequencing errors coupled with the particular algorithms and databases used to annotate the genome can result in significantly different annotations for the same genome. For example, upon reanalysis of the genome of *Mycoplasma pneumoniae* using more rigorous sequence comparisons coupled with molecular biological techniques, such as gel electrophoresis and mass spectrometry, researchers were able to identify several previously unidentified coding sequences, to dismiss a previous identified coding sequence as a likely pseudogene, and to adjust the length of several previously defined ORFs (Dandkar et al. (2000) Nucl. Acids Res. 28(17): 3278-3288). Furthermore, while overall conservation between amino acid sequences generally indicates a conservation of structure and function, specific changes at key residues can lead to significant variation in the biochemical and biophysical properties of a protein. In a comparison of three different functional annotations of the *Mycoplasma genitalium* genome, it was discovered that some genes were assigned three different functions and it was estimated that the overall error rate in the annotations was at least 8% (Brenner (1999) Trends Genet 15(4): 132-3). Accordingly, molecular biological techniques are required to ensure proper genome annotation and identify valid drug targets.

However, confirmation of genome annotation using molecular biological techniques is not an easy proposition due to the unpredictability in expression and purification of polypeptide sequences. Further, in order to carry out structural studies to validate proteins as potential drug targets, it is generally necessary to modify the native proteins in order to facilitate these analyses, e.g., by labeling the protein (e.g., with a heavy atom, isotopic label, polypeptide tag, etc.) or by creating fragments of the polypeptide corresponding to functional domains of a multi-domain protein. Moreover, it is well-known that even small changes in the amino acid sequence of a protein may lead to dramatic affects on protein solubility (Eberstadt et al. (1998) Nature 392: 941-945). Accordingly, genome-wide validation of protein targets will require considerable effort even in light of the sequence of the entire genome of an organism and/or purification conditions for homologs of a particular target.

We have developed reliable, high throughput methods to address some of the shortcomings identified above. In part, using these methods, we have now identified, expressed, and purified a novel antimicrobial target from *Enterococcus faecalis*, or *E.*

faecalis. Various biophysical, bioinformatic and biochemical studies have been used to characterize the structure and function of the polypeptides of the invention.

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20 SUMMARY OF THE INVENTION

As part of an effort at genome-wide structural and functional characterization of microbial targets, the present invention provides polypeptides from *E. faecalis*. In various aspects, the invention provides the nucleic acid and amino acid sequences of the polypeptides of the invention. The invention also provides purified, soluble forms of the polypeptides of the invention suitable for structural and functional characterization using a variety of techniques, including, for example, affinity chromatography, mass spectrometry, NMR and x-ray crystallography. The invention further provides modified versions of the polypeptides of the invention to facilitate characterization, including polypeptides labeled with isotopic or heavy atoms and fusion proteins.

30 A polypeptide of the invention has been crystallized and its structure solved as described in detail below, thereby providing information about the structure of the polypeptide, and druggable regions, domains and the like contained therein, all of which may be used in rational-based drug design efforts.

In general, the biological activity of a polypeptide of the invention is expected to be characterized as having a biochemical activity substantially similar to that of histidine tRNA synthetase, having the gene designation of *hisS*, as described in more detail below.

This assignment has been confirmed by solving the X-ray structure of a polypeptide of the invention.

5 All of the information learned and described herein about the polypeptides of the invention may be used to design modulators of one or more of their biological activities. In particular, information critical to the design of therapeutic and diagnostic molecules, including, for example, the protein domain, druggable regions, structural information, and the like for the polypeptides of the invention is now available or attainable as a result of the ability to prepare, purify and characterize them, and domains, fragments, variants and derivatives thereof.

10 In other aspects of the invention, structural and functional information about the polypeptides of the invention has and will be obtained. Such information, for example, may be incorporated into databases containing information on the polypeptides of the invention, as well as other polypeptide targets from other microbial species. Such databases will provide investigators with a powerful tool to analyze the polypeptides of the invention and aid in the rapid discovery and design of therapeutic and diagnostic molecules.

15 In another aspect, modulators, inhibitors, agonists or antagonists against the polypeptides of the invention, or biological complexes containing them, or orthologues thereto, may be used to treat any disease or other treatable condition of a patient (including humans and animals), and particularly a disease caused by *E. faecalis*, such as, for example, one of the following: urinary tract infection, surgical wound infection, bacteremia, intra abdominal infection, pelvic infection, central nervous system infection, osteomyelitis, pulmonary infection, and endocarditis.

25 The present invention further allows relationships between polypeptides from the same and multiple species to be compared by isolating and studying the various polypeptides of the invention and other proteins. By such comparison studies, which may involve multi-variable analysis as appropriate, it is possible to identify drugs that will affect multiple species or drugs that will affect one or a few species. In such a manner, so-called "wide spectrum" and narrow spectrum" anti-infectives may be identified. Alternatively, drugs that are selective for one or more bacterial or other non-mammalian species, and not for one or more mammalian species (especially human), may be identified (and vice-versa).

30 In other embodiments, the invention contemplates kits including the subject nucleic acids, polypeptides, crystallized polypeptides, antibodies, and other subject materials, and

optionally instructions for their use. Uses for such kits include, for example, diagnostic and therapeutic applications.

The embodiments and practices of the present invention, other embodiments, and their features and characteristics, will be apparent from the description, figures and claims
5 that follow, with all of the claims hereby being incorporated by this reference into this Summary.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 shows the nucleic acid coding sequence for an exemplary polypeptide of
10 the invention as predicted from the genomic sequence of *E. faecalis* (SEQ ID NO: 1). This predicted nucleic acid coding sequence was cloned and sequenced to produce the polynucleotide sequence shown in FIGURE 2 (SEQ ID NO: 3).

FIGURE 2 shows the amino acid sequence for an exemplary polypeptide of the invention as predicted from the nucleotide sequence shown in FIGURE 1 (SEQ ID NO: 2).

15 FIGURE 3 shows the experimentally determined nucleic acid coding sequence for an exemplary polypeptide of the invention (SEQ ID NO: 3).

FIGURE 4 shows the amino acid sequence for the exemplary polypeptide of the invention as predicted from the nucleotide sequence shown in FIGURE 3 (SEQ ID NO: 4).

FIGURE 5 shows the primer sequences used to amplify the nucleic acid of SEQ ID
20 NO: 3. The primers are SEQ ID NO: 5 and SEQ ID NO: 6.

FIGURE 6 contains Table 1, which provides among other things a variety of data and other information on the polypeptides of the invention.

FIGURE 7 contains Table 2, which provides the results of several bioinformatic analyses relating to SEQ ID NO: 2.

25 FIGURE 8 depicts the results of tryptic peptide mass spectrum peak searching as described in EXAMPLE 9.

FIGURE 9 depicts a MALDI-TOF mass spectrum of an intact polypeptide of the invention as described in EXAMPLE 10.

FIGURE 10 contains Table 3, which shows information related to the x-ray
30 structure for a polypeptide of the invention as described more fully in EXAMPLE 16.

FIGURE 11 lists the atomic structure coordinates for a polypeptide of the invention derived from x-ray diffraction from a crystal of such polypeptide, as described in more detail in EXAMPLE 16. There are multiple pages to FIGURE 11, labeled 1, 2, 3, etc. The information in such Figure is presented in the following tabular format, with a generic entry

5 provided as an example:

Record Header	No.	Atom Type	Residue	Residue Number	X	Y	Z	OCC	B
ATOM 1	1	CB	HIS	1	4.497	15.607	34.172	1	70.54

In the table, "Record Header" describes the row type, such as "ATOM". "No." refers to the row number. The first "Atom Type" column refers to the atom whose coordinates are measured, with the first letter in the column identifying the atom by its elemental symbol and the subsequent letter defining the location of the atom in the amino acid residue or other molecule. "Residue" and "residue number" identifies the residue of the subject polypeptide. "X, Y, Z" crystallographically define the atomic position of the atom measured. "Occ" is an occupancy factor that refers to the fraction of the molecules in which each atom occupies the position specified by the coordinates. A value of "1" indicates that each atom has the same conformation, i.e., the same position, in all molecules of the crystal. "B" is a thermal factor that is related to the root mean square deviation in the position of the atom around the given atomic coordinate.

FIGURE 12 depicts an alignment of the inferred amino acid sequence of *HisS* from six selected bacterial pathogens. Abbreviations: PA - *Pseudomonas aeruginosa*, EC - *Escherichia coli*, SA - *Staphylococcus aureus*, SP *Streptococcus pneumonia*, HP - *Heliobacter pylori* and EF *Enterococcus faecalis*.

FIGURE 13 depicts various views of the structure of the *E. faecalis HisS* molecule. FIGURE 13A depicts a ribbon diagram of the dimer of *HisS*, monomer A is colored blue, monomer (B) is colored red. FIGURE 13B depicts a ribbon diagram of the monomer of *HisS*. The N-terminal catalytic domain (Met1-Asp168, Leu227-Glu319) is colored green, the C-terminal domain (Leu330-Lys420) is colored yellow, the helical insertion domain (Met169-Phe226) is colored magenta and the small interface (SI) motif (Phe43-Leu77) is colored light blue. The histidine residues, likely from the cleaved histidine tag, are shown as blue sticks. All figures were produced in Pymol (Warren Delano Scientific) unless otherwise noted.

FIGURE 14 depicts an overlay of the *E. faecalis* HisS monomer (blue) and the *T. thermophilus* HisS monomer with histidine bound (PDB ID 1ADJ, in green).

FIGURE 15 depicts the predicted binding sites of HisS. FIGURE 15A depicts a ribbon diagram of the histidine binding site with the shape of the binding pocket shown as a mesh, with hydrophobic areas colored pink and hydrophilic area colored green. FIGURE 15B depicts a closer view of the protein showing the binding site for histidine with the binding site residues noted. Carbon atoms are light gray, oxygen, nitrogen and sulfur atoms are a darker shade of gray. FIGURE 15C depicts residues surrounding the binding pocket of histidine and the histidine found in the structure of *E. faecalis* HisS. FIGURE 15D depicts a comparison of the residues binding histidine in the *T. thermophilus* HisS structure (PDB ID:1ADJ) and *E. faecalis* HisS. The side chains of the *T. thermophilus* structure are green, except the histidines, which are yellow, and the *E. faecalis* structure is in gray. The overlay is based on a C α overlay (r.m.s.d. 1.39) so the overlay of the side chains in the binding pocket is slightly distorted.

FIGURE 16 depicts various views of the conservation of the HisS amino acid sequence mapped onto the *E. faecalis* HisS protein structure. The HisS amino acid sequence from six pathogenic bacteria species - the *P. aeruginosa*, *E. coli*, *S. aureus*, *S. pneumonia*, *H. pylori* and *E. faecalis* - were aligned in ClustalX and the conservation of each position was evaluated in Consurf. The sequence conservation metric was then projected onto the *E. faecalis* HisS protein structure, with the convention that red residues are invariant, pink residues are somewhat variable but generally well conserved (with the degree of pinkness correlating with the degree of conservation), white residues show an average degree of conservation for that set, and blue residues are hyper-variable. FIGURE 16A depicts the conservation mapped onto a solvent accessible surface view of the dimer structure. FIGURE 16B depicts the conservation mapped onto a ribbon diagram of the monomer and the histidine binding residues.

DETAILED DESCRIPTION OF THE INVENTION

1. Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

5 The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing.

10 The term "binding" refers to an association, which may be a stable association, between two molecules, e.g., between a polypeptide of the invention and a binding partner, due to, for example, electrostatic, hydrophobic, ionic and/or hydrogen-bond interactions under physiological conditions.

A "comparison window," as used herein, refers to a conceptual segment of at least
15 20 contiguous amino acid positions wherein a protein sequence may be compared to a reference sequence of at least 20 contiguous amino acids and wherein the portion of the protein sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of
20 sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2: 482, by the homology alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48: 443, by the search for similarity method of Pearson and Lipman (1988) Proc. Natl. Acad. Sci. (U.S.A.) 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and
25 TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection, and the best alignment (i.e., resulting in the highest percentage of homology over the comparison window) generated by the various methods may be identified.

The term "complex" refers to an association between at least two moieties (e.g.
30 chemical or biochemical) that have an affinity for one another. Examples of complexes include associations between antigen/antibodies, lectin/avidin, target polynucleotide/probe oligonucleotide, antibody/anti-antibody, receptor/ligand, enzyme/ligand, polypeptide/polypeptide, polypeptide/polynucleotide, polypeptide/co-factor, polypeptide/substrate,

polypeptide/inhibitor, polypeptide/small molecule, and the like. "Member of a complex" refers to one moiety of the complex, such as an antigen or ligand. "Protein complex" or "polypeptide complex" refers to a complex comprising at least one polypeptide.

The term "conserved residue" refers to an amino acid that is a member of a group of amino acids having certain common properties. The term "conservative amino acid substitution" refers to the substitution (conceptually or otherwise) of an amino acid from one such group with a different amino acid from the same group. A functional way to define common properties between individual amino acids is to analyze the normalized frequencies of amino acid changes between corresponding proteins of homologous organisms (Schulz, G. E. and R. H. Schirmer., Principles of Protein Structure, Springer-Verlag). According to such analyses, groups of amino acids may be defined where amino acids within a group exchange preferentially with each other, and therefore resemble each other most in their impact on the overall protein structure (Schulz, G. E. and R. H. Schirmer, Principles of Protein Structure, Springer-Verlag). One example of a set of amino acid groups defined in this manner include: (i) a charged group, consisting of Glu and Asp, Lys, Arg and His, (ii) a positively-charged group, consisting of Lys, Arg and His, (iii) a negatively-charged group, consisting of Glu and Asp, (iv) an aromatic group, consisting of Phe, Tyr and Trp, (v) a nitrogen ring group, consisting of His and Trp, (vi) a large aliphatic nonpolar group, consisting of Val, Leu and Ile, (vii) a slightly-polar group, consisting of Met and Cys, (viii) a small-residue group, consisting of Ser, Thr, Asp, Asn, Gly, Ala, Glu, Gln and Pro, (ix) an aliphatic group consisting of Val, Leu, Ile, Met and Cys, and (x) a small hydroxyl group consisting of Ser and Thr.

The term "domain", when used in connection with a polypeptide, refers to a specific region within such polypeptide that comprises a particular structure or mediates a particular function. In the typical case, a domain of a polypeptide of the invention is a fragment of the polypeptide. In certain instances, a domain is a structurally stable domain, as evidenced, for example, by mass spectroscopy, or by the fact that a modulator may bind to a druggable region of the domain.

The term "druggable region", when used in reference to a polypeptide, nucleic acid, complex and the like, refers to a region of the molecule which is a target or is a likely target for binding a modulator. For a polypeptide, a druggable region generally refers to a region wherein several amino acids of a polypeptide would be capable of interacting with a modulator or other molecule. For a polypeptide or complex thereof, exemplary druggable

regions including binding pockets and sites, enzymatic active sites, interfaces between domains of a polypeptide or complex, surface grooves or contours or surfaces of a polypeptide or complex which are capable of participating in interactions with another molecule. In certain instances, the interacting molecule is another polypeptide, which may
5 be naturally-occurring. In other instances, the druggable region is on the surface of the molecule.

Druggable regions may be described and characterized in a number of ways. For example, a druggable region may be characterized by some or all of the amino acids that make up the region, or the backbone atoms thereof, or the side chain atoms thereof
10 (optionally with or without the C α atoms). Alternatively, in certain instances, the volume of a druggable region corresponds to that of a carbon based molecule of at least about 200 amu and often up to about 800 amu. In other instances, it will be appreciated that the volume of such region may correspond to a molecule of at least about 600 amu and often up to about 1600 amu or more.

15 Alternatively, a druggable region may be characterized by comparison to other regions on the same or other molecules. For example, the term "affinity region" refers to a druggable region on a molecule (such as a polypeptide of the invention) that is present in several other molecules, in so much as the structures of the same affinity regions are sufficiently the same so that they are expected to bind the same or related structural
20 analogs. An example of an affinity region is an ATP-binding site of a protein kinase that is found in several protein kinases (whether or not of the same origin). The term "selectivity region" refers to a druggable region of a molecule that may not be found on other molecules, in so much as the structures of different selectivity regions are sufficiently different so that they are not expected to bind the same or related structural analogs. An
25 exemplary selectivity region is a catalytic domain of a protein kinase that exhibits specificity for one substrate. In certain instances, a single modulator may bind to the same affinity region across a number of proteins that have a substantially similar biological function, whereas the same modulator may bind to only one selectivity region of one of those proteins.

30 Continuing with examples of different druggable regions, the term "undesired region" refers to a druggable region of a molecule that upon interacting with another molecule results in an undesirable affect. For example, a binding site that oxidizes the interacting molecule (such as P-450 activity) and thereby results in increased toxicity for

the oxidized molecule may be deemed a "undesired region". Other examples of potential undesired regions includes regions that upon interaction with a drug decrease the membrane permeability of the drug, increase the excretion of the drug, or increase the blood brain transport of the drug. It may be the case that, in certain circumstances, an undesired region will no longer be deemed an undesired region because the affect of the region will be favorable, e.g., a drug intended to treat a brain condition would benefit from interacting with a region that resulted in increased blood brain transport, whereas the same region could be deemed undesirable for drugs that were not intended to be delivered to the brain.

When used in reference to a druggable region, the "selectivity" or "specificity" of a molecule such as a modulator to a druggable region may be used to describe the binding between the molecule and a druggable region. For example, the selectivity of a modulator with respect to a druggable region may be expressed by comparison to another modulator, using the respective values of K_d (i.e., the dissociation constants for each modulator-druggable region complex) or, in cases where a biological effect is observed below the K_d , the ratio of the respective EC_{50} 's (i.e., the concentrations that produce 50% of the maximum response for the modulator interacting with each druggable region).

A "fusion protein" or "fusion polypeptide" refers to a chimeric protein as that term is known in the art and may be constructed using methods known in the art. In many examples of fusion proteins, there are two different polypeptide sequences, and in certain cases, there may be more. The sequences may be linked in frame. A fusion protein may include a domain which is found (albeit in a different protein) in an organism which also expresses the first protein, or it may be an "interspecies", "intergenic", etc. fusion expressed by different kinds of organisms. In various embodiments, the fusion polypeptide may comprise one or more amino acid sequences linked to a first polypeptide. In the case where more than one amino acid sequence is fused to a first polypeptide, the fusion sequences may be multiple copies of the same sequence, or alternatively, may be different amino acid sequences. The fusion polypeptides may be fused to the N-terminus, the C-terminus, or the N- and C-terminus of the first polypeptide. Exemplary fusion proteins include polypeptides comprising a glutathione S-transferase tag (GST-tag), histidine tag (His-tag), an immunoglobulin domain or an immunoglobulin binding domain.

The term "gene" refers to a nucleic acid comprising an open reading frame encoding a polypeptide having exon sequences and optionally intron sequences. The term "intron"

refers to a DNA sequence present in a given gene which is not translated into protein and is generally found between exons.

The term "having substantially similar biological activity", when used in reference to two polypeptides, refers to a biological activity of a first polypeptide which is substantially similar to at least one of the biological activities of a second polypeptide. A substantially similar biological activity means that the polypeptides carry out a similar function, e.g., a similar enzymatic reaction or a similar physiological process, etc. For example, two homologous proteins may have a substantially similar biological activity if they are involved in a similar enzymatic reaction, e.g., they are both kinases which catalyze phosphorylation of a substrate polypeptide, however, they may phosphorylate different regions on the same protein substrate or different substrate proteins altogether. Alternatively, two homologous proteins may also have a substantially similar biological activity if they are both involved in a similar physiological process, e.g., transcription. For example, two proteins may be transcription factors, however, they may bind to different DNA sequences or bind to different polypeptide interactors. Substantially similar biological activities may also be associated with proteins carrying out a similar structural role, for example, two membrane proteins.

The term "isolated polypeptide" refers to a polypeptide, in certain embodiments prepared from recombinant DNA or RNA, or of synthetic origin, or some combination thereof, which (1) is not associated with proteins that it is normally found with in nature, (2) is isolated from the cell in which it normally occurs, (3) is isolated free of other proteins from the same cellular source, e.g. free of other *E. faecalis* proteins, (4) is expressed by a cell from a different species, or (5) does not occur in nature.

The term "isolated nucleic acid" refers to a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which (1) is not associated with the cell in which the "isolated nucleic acid" is found in nature, or (2) is operably linked to a polynucleotide to which it is not linked in nature.

The terms "label" or "labeled" refer to incorporation or attachment, optionally covalently or non-covalently, of a detectable marker into a molecule, such as a polypeptide. Various methods of labeling polypeptides are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes, fluorescent labels, heavy atoms, enzymatic labels or reporter genes, chemiluminescent groups, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary

reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). Examples and use of such labels are described in more detail below. In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

5 The term "mammal" is known in the art, and exemplary mammals include humans, primates, bovines, porcines, canines, felines, and rodents (e.g., mice and rats).

 The term "modulation", when used in reference to a functional property or biological activity or process (e.g., enzyme activity or receptor binding), refers to the capacity to either up regulate (e.g., activate or stimulate), down regulate (e.g., inhibit or
10 suppress) or otherwise change a quality of such property, activity or process. In certain instances, such regulation may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or may be manifest only in particular cell types.

 The term "modulator" refers to a polypeptide, nucleic acid, macromolecule,
15 complex, molecule, small molecule, compound, species or the like (naturally-occurring or non-naturally-occurring), or an extract made from biological materials such as bacteria, plants, fungi, or animal cells or tissues, that may be capable of causing modulation. Modulators may be evaluated for potential activity as inhibitors or activators (directly or indirectly) of a functional property, biological activity or process, or combination of them,
20 (e.g., agonist, partial antagonist, partial agonist, inverse agonist, antagonist, anti-microbial agents, inhibitors of microbial infection or proliferation, and the like) by inclusion in assays. In such assays, many modulators may be screened at one time. The activity of a modulator may be known, unknown or partially known.

 The term "motif" refers to an amino acid sequence that is commonly found in a
25 protein of a particular structure or function. Typically, a consensus sequence is defined to represent a particular motif. The consensus sequence need not be strictly defined and may contain positions of variability, degeneracy, variability of length, etc. The consensus sequence may be used to search a database to identify other proteins that may have a similar structure or function due to the presence of the motif in its amino acid sequence. For
30 example, on-line databases may be searched with a consensus sequence in order to identify other proteins containing a particular motif. Various search algorithms and/or programs may be used, including FASTA, BLAST or ENTREZ. FASTA and BLAST are available as a part of the GCG sequence analysis package (University of Wisconsin, Madison, Wis.).

ENTREZ is available through the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD.

The term "naturally-occurring", as applied to an object, refers to the fact that an object may be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including bacteria) that may be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

The term "nucleic acid" refers to a polymeric form of nucleotides, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The terms should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single-stranded (such as sense or antisense) and double-stranded polynucleotides.

The term "nucleic acid of the invention" refers to a nucleic acid encoding a polypeptide of the invention, e.g., a nucleic acid comprising a sequence consisting of, or consisting essentially of, the polynucleotide sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3. A nucleic acid of the invention may comprise all, or a portion of: the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3; a nucleotide sequence at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 1 or SEQ ID NO: 3; a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3; nucleotide sequences encoding polypeptides that are functionally equivalent to polypeptides of the invention; nucleotide sequences encoding polypeptides at least about 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99% homologous or identical with an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4; nucleotide sequences encoding polypeptides having an activity of a polypeptide of the invention and having at least about 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99% or more homology or identity with SEQ ID NO: 2 or SEQ ID NO: 4; nucleotide sequences that differ by 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more nucleotide substitutions, additions or deletions, such as allelic variants, of SEQ ID NO: 1 and SEQ ID NO: 3; nucleic acids derived from and evolutionarily related to SEQ ID NO: 1 or SEQ ID NO: 3; and complements of, and nucleotide sequences resulting from the degeneracy of the genetic code, for all of the foregoing and other nucleic acids of the invention. Nucleic acids of the invention also include homologs, e.g., orthologs and paralogs, of SEQ ID NO: 1 or SEQ ID NO: 3 and also variants of SEQ ID NO: 1 or SEQ ID NO: 3.

NO: 3 which have been codon optimized for expression in a particular organism (e.g., host cell).

The term "operably linked", when describing the relationship between two nucleic acid regions, refers to a juxtaposition wherein the regions are in a relationship permitting them to function in their intended manner. For example, a control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences, such as when the appropriate molecules (e.g., inducers and polymerases) are bound to the control or regulatory sequence(s).

The term "phenotype" refers to the entire physical, biochemical, and physiological makeup of a cell, e.g., having any one trait or any group of traits.

The term "polypeptide", and the terms "protein" and "peptide" which are used interchangeably herein, refers to a polymer of amino acids. Exemplary polypeptides include gene products, naturally-occurring proteins, homologs, orthologs, paralogs, fragments, and other equivalents, variants and analogs of the foregoing.

The terms "polypeptide fragment" or "fragment", when used in reference to a reference polypeptide, refers to a polypeptide in which amino acid residues are deleted as compared to the reference polypeptide itself, but where the remaining amino acid sequence is usually identical to the corresponding positions in the reference polypeptide. Such deletions may occur at the amino-terminus or carboxy-terminus of the reference polypeptide, or alternatively both. Fragments typically are at least 5, 6, 8 or 10 amino acids long, at least 14 amino acids long, at least 20, 30, 40 or 50 amino acids long, at least 75 amino acids long, or at least 100, 150, 200, 300, 500 or more amino acids long. A fragment can retain one or more of the biological activities of the reference polypeptide. In certain embodiments, a fragment may comprise a druggable region, and optionally additional amino acids on one or both sides of the druggable region, which additional amino acids may number from 5, 10, 15, 20, 30, 40, 50, or up to 100 or more residues. Further, fragments can include a sub-fragment of a specific region, which sub-fragment retains a function of the region from which it is derived. In another embodiment, a fragment may have immunogenic properties.

The term "polypeptide of the invention" refers to a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, or an equivalent or

fragment thereof, e.g., a polypeptide comprising a sequence consisting of, or consisting essentially of, the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4. Polypeptides of the invention include polypeptides comprising all or a portion of the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 with 1 to about 2, 3, 5, 7, 10, 15, 20, 30, 50, 75 or more conservative amino acid substitutions; an amino acid sequence that is at least 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 2 or SEQ ID NO: 4; and functional fragments thereof. Polypeptides of the invention also include homologs, e.g., orthologs and paralogs, of SEQ ID NO: 2 or SEQ ID NO: 4.

10 The term "purified" refers to an object species that is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition). A "purified fraction" is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all species present. In making the determination of the purity of a species in solution or dispersion, the solvent or matrix in which the species is dissolved or dispersed is usually not included in such determination; instead, only the species (including the one of interest) dissolved or dispersed are taken into account. Generally, a purified composition will have one species that comprises more than about 80 percent of all species present in the composition, more than about 85%, 90%, 95%, 99% or more of all species present. The object species may be purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single species. A skilled artisan may purify a polypeptide of the invention using standard techniques for protein purification in light of the teachings herein. Purity of a polypeptide may be determined by a number of methods known to those of skill in the art, including for example, amino-terminal amino acid sequence analysis, gel electrophoresis, mass-spectrometry analysis and the methods described in the Exemplification section herein.

25 The terms "recombinant protein" or "recombinant polypeptide" refer to a polypeptide which is produced by recombinant DNA techniques. An example of such techniques includes the case when DNA encoding the expressed protein is inserted into a suitable expression vector which is in turn used to transform a host cell to produce the protein or polypeptide encoded by the DNA.

A "reference sequence" is a defined sequence used as a basis for a sequence comparison; a reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length protein given in a sequence listing such as SEQ ID NO: 2 or SEQ ID NO: 4, or may comprise a complete protein sequence. Generally, a reference sequence
5 is at least 200, 300 or 400 nucleotides in length, frequently at least 600 nucleotides in length, and often at least 800 nucleotides in length (or the protein equivalent if it is shorter or longer in length). Because two proteins may each (1) comprise a sequence (i.e., a portion of the complete protein sequence) that is similar between the two proteins, and (2) may further comprise a sequence that is divergent between the two proteins, sequence
10 comparisons between two (or more) proteins are typically performed by comparing sequences of the two proteins over a "comparison window" to identify and compare local regions of sequence similarity.

The term "regulatory sequence" is a generic term used throughout the specification to refer to polynucleotide sequences, such as initiation signals, enhancers, regulators and
15 promoters, that are necessary or desirable to affect the expression of coding and non-coding sequences to which they are operably linked. Exemplary regulatory sequences are described in Goeddel; *Gene Expression Technology: Methods in Enzymology*, Academic Press, San Diego, CA (1990), and include, for example, the early and late promoters of SV40, adenovirus or cytomegalovirus immediate early promoter, the lac system, the trp
20 system, the TAC or TRC system, T7 promoter whose expression is directed by T7 RNA polymerase, the major operator and promoter regions of phage lambda, the control regions for fd coat protein, the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase, e.g., Pho5, the promoters of the yeast α -mating factors, the polyhedron promoter of the baculovirus system and other sequences known to control
25 the expression of genes of prokaryotic or eukaryotic cells or their viruses, and various combinations thereof. The nature and use of such control sequences may differ depending upon the host organism. In prokaryotes, such regulatory sequences generally include promoter, ribosomal binding site, and transcription termination sequences. The term "regulatory sequence" is intended to include, at a minimum, components whose presence
30 may influence expression, and may also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. In certain embodiments, transcription of a polynucleotide sequence is under the control of a promoter sequence (or other regulatory sequence) which controls the expression of the

polynucleotide in a cell-type in which expression is intended. It will also be understood that the polynucleotide can be under the control of regulatory sequences which are the same or different from those sequences which control expression of the naturally-occurring form of the polynucleotide.

- 5 The term "reporter gene" refers to a nucleic acid comprising a nucleotide sequence encoding a protein that is readily detectable either by its presence or activity, including, but not limited to, luciferase, fluorescent protein (e.g., green fluorescent protein), chloramphenicol acetyl transferase, β -galactosidase, secreted placental alkaline phosphatase, β -lactamase, human growth hormone, and other secreted enzyme reporters.
- 10 Generally, a reporter gene encodes a polypeptide not otherwise produced by the host cell, which is detectable by analysis of the cell(s), e.g., by the direct fluorometric, radioisotopic or spectrophotometric analysis of the cell(s) and preferably without the need to kill the cells for signal analysis. In certain instances, a reporter gene encodes an enzyme, which produces a change in fluorometric properties of the host cell, which is detectable by
- 15 qualitative, quantitative or semiquantitative function or transcriptional activation. Exemplary enzymes include esterases, β -lactamase, phosphatases, peroxidases, proteases (tissue plasminogen activator or urokinase) and other enzymes whose function may be detected by appropriate chromogenic or fluorogenic substrates known to those skilled in the art or developed in the future.
- 20 The term "sequence homology" refers to the proportion of base matches between two nucleic acid sequences or the proportion of amino acid matches between two amino acid sequences. When sequence homology is expressed as a percentage, e.g., 50%, the percentage denotes the proportion of matches over the length of sequence from a desired sequence (e.g., SEQ. ID NO: 1) that is compared to some other sequence. Gaps (in either
- 25 of the two sequences) are permitted to maximize matching; gap lengths of 15 bases or less are usually used, 6 bases or less are used more frequently, with 2 bases or less used even more frequently. The term "sequence identity" means that sequences are identical (i.e., on a nucleotide-by-nucleotide basis for nucleic acids or amino acid-by-amino acid basis for polypeptides) over a window of comparison. The term "percentage of sequence identity" is
- 30 calculated by comparing two optimally aligned sequences over the comparison window, determining the number of positions at which the identical amino acids occurs in both sequences to yield the number of matched positions, dividing the number of matched

positions by the total number of positions in the comparison window, and multiplying the result by 100 to yield the percentage of sequence identity. Methods to calculate sequence identity are known to those of skill in the art and described in further detail below.

The term "small molecule" refers to a compound, which has a molecular weight of
5 less than about 5 kD, less than about 2.5 kD, less than about 1.5 kD, or less than about 0.9 kD. Small molecules may be, for example, nucleic acids, peptides, polypeptides, peptide nucleic acids, peptidomimetics, carbohydrates, lipids or other organic (carbon containing) or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be
10 screened with any of the assays of the invention. The term "small organic molecule" refers to a small molecule that is often identified as being an organic or medicinal compound, and does not include molecules that are exclusively nucleic acids, peptides or polypeptides.

The term "soluble" as used herein with reference to a polypeptide of the invention or other protein, means that upon expression in cell culture, at least some portion of the
15 polypeptide or protein expressed remains in the cytoplasmic fraction of the cell and does not fractionate with the cellular debris upon lysis and centrifugation of the lysate. Solubility of a polypeptide may be increased by a variety of art recognized methods, including fusion to a heterologous amino acid sequence, deletion of amino acid residues, amino acid substitution (e.g., enriching the sequence with amino acid residues having
20 hydrophilic side chains), and chemical modification (e.g., addition of hydrophilic groups). The solubility of polypeptides may be measured using a variety of art recognized techniques, including, dynamic light scattering to determine aggregation state, UV absorption, centrifugation to separate aggregated from non-aggregated material, and SDS gel electrophoresis (e.g., the amount of protein in the soluble fraction is compared to the
25 amount of protein in the soluble and insoluble fractions combined). When expressed in a host cell, the polypeptides of the invention may be at least about 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more soluble, e.g., at least about 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more of the total amount of protein expressed in the cell is found in the cytoplasmic fraction. In certain embodiments, a one
30 liter culture of cells expressing a polypeptide of the invention will produce at least about 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 30, 40, 50 milligrams or more of soluble protein. In an exemplary embodiment, a polypeptide of the invention is at least about 10% soluble and will produce at least about 1 milligram of protein from a one liter cell culture.

The term "specifically hybridizes" refers to detectable and specific nucleic acid binding. Polynucleotides, oligonucleotides and nucleic acids of the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. Stringent conditions may be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides, and nucleic acids of the invention and a nucleic acid sequence of interest will be at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, 99%, or more. In certain instances, hybridization and washing conditions are performed under stringent conditions according to conventional hybridization procedures and as described further herein.

The terms "stringent conditions" or "stringent hybridization conditions" refer to conditions which promote specific hybridization between two complementary polynucleotide strands so as to form a duplex. Stringent conditions may be selected to be about 5°C lower than the thermal melting point (T_m) for a given polynucleotide duplex at a defined ionic strength and pH. The length of the complementary polynucleotide strands and their GC content will determine the T_m of the duplex, and thus the hybridization conditions necessary for obtaining a desired specificity of hybridization. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the a polynucleotide sequence hybridizes to a perfectly matched complementary strand. In certain cases it may be desirable to increase the stringency of the hybridization conditions to be about equal to the T_m for a particular duplex.

A variety of techniques for estimating the T_m are available. Typically, G-C base pairs in a duplex are estimated to contribute about 3°C to the T_m, while A-T base pairs are estimated to contribute about 2°C, up to a theoretical maximum of about 80-100°C. However, more sophisticated models of T_m are available in which G-C stacking interactions, solvent effects, the desired assay temperature and the like are taken into account. For example, probes can be designed to have a dissociation temperature (T_d) of approximately 60°C, using the formula: $T_d = (((3 \times \#GC) + (2 \times \#AT)) \times 37) - 562) / \#bp - 5$; where #GC, #AT, and #bp are the number of guanine-cytosine base pairs, the number of adenine-thymine base pairs, and the number of total base pairs, respectively, involved in the formation of the duplex.

Hybridization may be carried out in 5xSSC, 4xSSC, 3xSSC, 2xSSC, 1xSSC or 0.2xSSC for at least about 1 hour, 2 hours, 5 hours, 12 hours, or 24 hours. The temperature of the hybridization may be increased to adjust the stringency of the reaction, for example, from about 25°C (room temperature), to about 45°C, 50°C, 55°C, 60°C, or 65°C. The hybridization reaction may also include another agent affecting the stringency, for example, hybridization conducted in the presence of 50% formamide increases the stringency of hybridization at a defined temperature.

The hybridization reaction may be followed by a single wash step, or two or more wash steps, which may be at the same or a different salinity and temperature. For example, the temperature of the wash may be increased to adjust the stringency from about 25°C (room temperature), to about 45°C, 50°C, 55°C, 60°C, 65°C, or higher. The wash step may be conducted in the presence of a detergent, e.g., 0.1 or 0.2% SDS. For example, hybridization may be followed by two wash steps at 65°C each for about 20 minutes in 2xSSC, 0.1% SDS, and optionally two additional wash steps at 65°C each for about 20 minutes in 0.2xSSC, 0.1%SDS.

Exemplary stringent hybridization conditions include overnight hybridization at 65°C in a solution comprising, or consisting of, 50% formamide, 10xDenhardt (0.2% Ficoll, 0.2% Polyvinylpyrrolidone, 0.2% bovine serum albumin) and 200 µg/ml of denatured carrier DNA, e.g., sheared salmon sperm DNA, followed by two wash steps at 65°C each for about 20 minutes in 2xSSC, 0.1% SDS, and two wash steps at 65°C each for about 20 minutes in 0.2xSSC, 0.1%SDS.

Hybridization may consist of hybridizing two nucleic acids in solution, or a nucleic acid in solution to a nucleic acid attached to a solid support, e.g., a filter. When one nucleic acid is on a solid support, a prehybridization step may be conducted prior to hybridization. Prehybridization may be carried out for at least about 1 hour, 3 hours or 10 hours in the same solution and at the same temperature as the hybridization solution (without the complementary polynucleotide strand).

Appropriate stringency conditions are known to those skilled in the art or may be determined experimentally by the skilled artisan. See, for example, Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-12.3.6; Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, N.Y; S. Agrawal (ed.) Methods in Molecular Biology, volume 20; Tijssen (1993) Laboratory Techniques in biochemistry and molecular biology-hybridization with nucleic acid probes, e.g., part I

chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays", Elsevier, New York; and Tibanyenda, N. et al., Eur. J. Biochem. 139:19 (1984) and Ebel, S. et al., Biochem. 31:12083 (1992).

As applied to proteins, the term "substantial identity" means that two protein
5 sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, typically share at least about 70 percent sequence identity, alternatively at least about 80, 85, 90, 95 percent sequence identity or more. In certain instances, residue positions that are not identical differ by conservative amino acid substitutions, which are described above.

10 The term "structural motif", when used in reference to a polypeptide, refers to a polypeptide that, although it may have different amino acid sequences, may result in a similar structure, wherein by structure is meant that the motif forms generally the same tertiary structure, or that certain amino acid residues within the motif, or alternatively their backbone or side chains (which may or may not include the C α atoms of the side chains)
15 are positioned in a like relationship with respect to one another in the motif.

The term "test compound" refers to a molecule to be tested by one or more screening method(s) as a putative modulator of a polypeptide of the invention or other biological entity or process. A test compound is usually not known to bind to a target of interest. The term "control test compound" refers to a compound known to bind to the
20 target (e.g., a known agonist, antagonist, partial agonist or inverse agonist). The term "test compound" does not include a chemical added as a control condition that alters the function of the target to determine signal specificity in an assay. Such control chemicals or conditions include chemicals that 1) nonspecifically or substantially disrupt protein structure (e.g., denaturing agents (e.g., urea or guanidinium), chaotropic agents, sulfhydryl
25 reagents (e.g., dithiothreitol and β -mercaptoethanol), and proteases), 2) generally inhibit cell metabolism (e.g., mitochondrial uncouplers) and 3) non-specifically disrupt electrostatic or hydrophobic interactions of a protein (e.g., high salt concentrations, or detergents at concentrations sufficient to non-specifically disrupt hydrophobic interactions). Further, the term "test compound" also does not include compounds known to be unsuitable
30 for a therapeutic use for a particular indication due to toxicity of the subject. In certain embodiments, various predetermined concentrations of test compounds are used for screening such as 0.01 μ M, 0.1 μ M, 1.0 μ M, and 10.0 μ M. Examples of test compounds include, but are not limited to, peptides, nucleic acids, carbohydrates, and small molecules.

The term "novel test compound" refers to a test compound that is not in existence as of the filing date of this application. In certain assays using novel test compounds, the novel test compounds comprise at least about 50%, 75%, 85%, 90%, 95% or more of the test compounds used in the assay or in any particular trial of the assay.

5 The term "therapeutically effective amount" refers to that amount of a modulator, drug or other molecule which is sufficient to effect treatment when administered to a subject in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like,
10 which can readily be determined by one of ordinary skill in the art.

 The term "transfection" means the introduction of a nucleic acid, e.g., an expression vector, into a recipient cell, which in certain instances involves nucleic acid-mediated gene transfer. The term "transformation" refers to a process in which a cell's genotype is changed as a result of the cellular uptake of exogenous nucleic acid. For example, a
15 transformed cell may express a recombinant form of a polypeptide of the invention or antisense expression may occur from the transferred gene so that the expression of a naturally-occurring form of the gene is disrupted.

 The term "transgene" means a nucleic acid sequence, which is partly or entirely heterologous to a transgenic animal or cell into which it is introduced, or, is homologous to
20 an endogenous gene of the transgenic animal or cell into which it is introduced, but which is designed to be inserted, or is inserted, into the animal's genome in such a way as to alter the genome of the cell into which it is inserted (e.g., it is inserted at a location which differs from that of the natural gene or its insertion results in a knockout). A transgene may include one or more regulatory sequences and any other nucleic acids, such as introns, that
25 may be necessary for optimal expression.

 The term "transgenic animal" refers to any animal, for example, a mouse, rat or other non-human mammal, a bird or an amphibian, in which one or more of the cells of the animal contain heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell,
30 directly or indirectly, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or *in vitro* fertilization, but rather is directed to the introduction of a recombinant DNA molecule. This molecule may be integrated within a chromosome, or

it may be extrachromosomally replicating DNA. In the typical transgenic animals described herein, the transgene causes cells to express a recombinant form of a protein. However, transgenic animals in which the recombinant gene is silent are also contemplated.

The term "vector" refers to a nucleic acid capable of transporting another nucleic acid to which it has been linked. One type of vector which may be used in accord with the invention is an episome, i.e., a nucleic acid capable of extra-chromosomal replication. Other vectors include those capable of autonomous replication and expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer to circular double stranded DNA molecules which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

2. Polypeptides of the Invention

The present invention makes available in a variety of embodiments soluble, purified and/or isolated forms of the polypeptides of the invention. Milligram quantities of an exemplary polypeptide of the invention, SEQ ID NO: 4 (optionally with a tag, and optionally labeled), have been isolated in a highly purified form. The present invention provides for expressing and purifying polypeptides of the invention in quantities that equal or exceed the quantity of polypeptide(s) of the invention expressed and purified as provided in the Exemplification section below (or smaller amount(s) thereof, such as 25%, 33%, 50% or 75% of the amount(s) so expressed and/or purified).

In one aspect, the present invention contemplates an isolated polypeptide comprising (a) the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, (b)

the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4 with 1 to about 20 conservative amino acid substitutions, deletions or additions, (c) an amino acid sequence that is at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 4 or (d) a functional fragment of a polypeptide having an amino acid sequence set forth in (a), (b) or (c). In
5 another aspect, the present invention contemplates a composition comprising such an isolated polypeptide and less than about 10%, or alternatively 5%, or alternatively 1%, contaminating biological macromolecules or polypeptides.

It may be the case that the amino acid sequence of SEQ ID NO: 4 differs from that of SEQ ID NO: 2 by one or more amino acids. SEQ ID NO: 4 is determined from the
10 experimentally determined nucleic acid sequence SEQ ID NO: 3, and SEQ ID NO: 2 is determined from SEQ ID NO: 1, which is obtained as described in EXAMPLE 1. In such a case, the present invention contemplates the specific amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4, and variants thereof, as well as any differences (if any) in the polypeptides of the invention based on those SEQ ID NOS and nucleic acid sequences
15 encoding the same.

In certain embodiments, a polypeptide of the invention is a fusion protein containing a domain which increases its solubility and/or facilitates its purification, identification, detection, and/or structural characterization. Exemplary domains, include, for example, glutathione S-transferase (GST), protein A, protein G, calmodulin-binding peptide, thioredoxin, maltose binding protein, HA, myc, poly arginine, poly His, poly His-Asp or
20 FLAG fusion proteins and tags. Additional exemplary domains include domains that alter protein localization *in vivo*, such as signal peptides, type III secretion system-targeting peptides, transcytosis domains, nuclear localization signals, etc. In various embodiments, a polypeptide of the invention may comprise one or more heterologous fusions. Polypeptides
25 may contain multiple copies of the same fusion domain or may contain fusions to two or more different domains. The fusions may occur at the N-terminus of the polypeptide, at the C-terminus of the polypeptide, or at both the N- and C-terminus of the polypeptide. It is also within the scope of the invention to include linker sequences between a polypeptide of the invention and the fusion domain in order to facilitate construction of the fusion protein
30 or to optimize protein expression or structural constraints of the fusion protein. In another embodiment, the polypeptide may be constructed so as to contain protease cleavage sites between the fusion polypeptide and polypeptide of the invention in order to remove the tag

after protein expression or thereafter. Examples of suitable endoproteases, include, for example, Factor Xa and TEV proteases.

In another embodiment, a polypeptide of the invention may be modified so that its rate of traversing the cellular membrane is increased. For example, the polypeptide may be fused to a second peptide which promotes "transcytosis," e.g., uptake of the peptide by cells. The peptide may be a portion of the HIV transactivator (TAT) protein, such as the fragment corresponding to residues 37-62 or 48-60 of TAT, portions which have been observed to be rapidly taken up by a cell *in vitro* (Green and Loewenstein, (1989) Cell 55:1179-1188). Alternatively, the internalizing peptide may be derived from the *Drosophila antennapedia* protein, or homologs thereof. The 60 amino acid long homeodomain of the homeo-protein antennapedia has been demonstrated to translocate through biological membranes and can facilitate the translocation of heterologous polypeptides to which it is coupled. Thus, polypeptides may be fused to a peptide consisting of about amino acids 42-58 of *Drosophila antennapedia* or shorter fragments for transcytosis (Derossi et al. (1996) J Biol Chem 271:18188-18193; Derossi et al. (1994) J Biol Chem 269:10444-10450; and Perez et al. (1992) J Cell Sci 102:717-722). The transcytosis polypeptide may also be a non-naturally-occurring membrane-translocating sequence (MTS), such as the peptide sequences disclosed in U.S. Patent No. 6,248,558.

In another embodiment, a polypeptide of the invention is labeled with an isotopic label to facilitate its detection and or structural characterization using nuclear magnetic resonance or another applicable technique. Exemplary isotopic labels include radioisotopic labels such as, for example, potassium-40 (^{40}K), carbon-14 (^{14}C), tritium (^3H), sulphur-35 (^{35}S), phosphorus-32 (^{32}P), technetium-99m ($^{99\text{m}}\text{Tc}$), thallium-201 (^{201}Tl), gallium-67 (^{67}Ga), indium-111 (^{111}In), iodine-123 (^{123}I), iodine-131 (^{131}I), yttrium-90 (^{90}Y), samarium-153 (^{153}Sm), rhenium-186 (^{186}Re), rhenium-188 (^{188}Re), dysprosium-165 (^{165}Dy) and holmium-166 (^{166}Ho). The isotopic label may also be an atom with non zero nuclear spin, including, for example, hydrogen-1 (^1H), hydrogen-2 (^2H), hydrogen-3 (^3H), phosphorous-31 (^{31}P), sodium-23 (^{23}Na), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), carbon-13 (^{13}C) and fluorine-19 (^{19}F). In certain embodiments, the polypeptide is uniformly labeled with an isotopic label, for example, wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the possible labels in the polypeptide are labeled, e.g., wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the nitrogen atoms in the polypeptide are ^{15}N , and/or wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the carbon atoms in the polypeptide are ^{13}C , and/or

wherein at least 50%, 70%, 80%, 90%, 95%, or 98% of the hydrogen atoms in the polypeptide are ^2H . In other embodiments, the isotopic label is located in one or more specific locations within the polypeptide, for example, the label may be specifically incorporated into one or more of the leucine residues of the polypeptide. The invention also
5 encompasses the embodiment wherein a single polypeptide comprises two, three or more different isotopic labels, for example, the polypeptide comprises both ^{15}N and ^{13}C labeling.

In yet another embodiment, the polypeptides of the invention are labeled to facilitate structural characterization using x-ray crystallography or another applicable technique. Exemplary labels include heavy atom labels such as, for example, cobalt, selenium,
10 krypton, bromine, strontium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, tin, iodine, xenon, barium, lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, thorium and uranium. In an exemplary embodiment, the
15 polypeptide is labeled with seleno-methionine.

A variety of methods are available for preparing a polypeptide with a label, such as a radioisotopic label or heavy atom label. For example, in one such method, an expression vector comprising a nucleic acid encoding a polypeptide is introduced into a host cell, and the host cell is cultured in a cell culture medium in the presence of a source of the label,
20 thereby generating a labeled polypeptide. As indicated above, the extent to which a polypeptide may be labeled may vary.

In still another embodiment, the polypeptides of the invention are labeled with a fluorescent label to facilitate their detection, purification, or structural characterization. In an exemplary embodiment, a polypeptide of the invention is fused to a heterologous
25 polypeptide sequence which produces a detectable fluorescent signal, including, for example, green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), *Renilla Reniformis* green fluorescent protein, GFPmut2, GFPuv4, enhanced yellow fluorescent protein (EYFP), enhanced cyan fluorescent protein (ECFP), enhanced blue fluorescent protein (EBFP), citrine and red fluorescent protein from discosoma (dsRED).

30 In other embodiments, the invention provides for polypeptides of the invention immobilized onto a solid surface, including, microtiter plates, slides, beads, films, etc. The polypeptides of the invention may be immobilized onto a "chip" as part of an array. An array, having a plurality of addresses, may comprise one or more polypeptides of the

invention in one or more of those addresses. In one embodiment, the chip comprises one or more polypeptides of the invention as part of an array of *E. faecalis* polypeptide sequences.

In other embodiments, the invention provides for polypeptides of the invention immobilized onto a solid surface, including, plates, microtiter plates, slides, beads, particles, spheres, films, strands, precipitates, gels, sheets, tubing, containers, capillaries, pads, slices, etc. The polypeptides of the invention may be immobilized onto a "chip" as part of an array. An array, having a plurality of addresses, may comprise one or more polypeptides of the invention in one or more of those addresses. In one embodiment, the chip comprises one or more polypeptides of the invention as part of an array that contains at least some polypeptide sequences from *E. faecalis*.

In still other embodiments, the invention comprises the polypeptide sequences of the invention in computer readable format. The invention also encompasses a database comprising the polypeptide sequences of the invention.

In other embodiments, the invention relates to the polypeptides of the invention contained within a vessels useful for manipulation of the polypeptide sample. For example, the polypeptides of the invention may be contained within a microtiter plate to facilitate detection, screening or purification of the polypeptide. The polypeptides may also be contained within a syringe as a container suitable for administering the polypeptide to a subject in order to generate antibodies or as part of a vaccination regimen. The polypeptides may also be contained within an NMR tube in order to enable characterization by nuclear magnetic resonance techniques.

In still other embodiments, the invention relates to a crystallized polypeptide of the invention and crystallized polypeptides which have been mounted for examination by x-ray crystallography as described further below. In certain instances, a polypeptide of the invention in crystal form may be single crystals of various dimensions (e.g., micro-crystals) or may be an aggregate of crystalline material. In another aspect, the present invention contemplates a crystallized complex including a polypeptide of the invention and one or more of the following: a co-factor (such as a salt, metal, nucleotide, oligonucleotide or polypeptide), a modulator, or a small molecule. In another aspect, the present invention contemplates a crystallized complex including a polypeptide of the invention and any other molecule or atom (such as a metal ion) that associates with the polypeptide *in vivo*.

In certain embodiments, polypeptides of the invention may be synthesized chemically, ribosomally in a cell free system, or ribosomally within a cell. Chemical

synthesis of polypeptides of the invention may be carried out using a variety of art recognized methods, including stepwise solid phase synthesis, semi-synthesis through the conformationally-assisted re-ligation of peptide fragments, enzymatic ligation of cloned or synthetic peptide segments, and chemical ligation. Native chemical ligation employs a chemoselective reaction of two unprotected peptide segments to produce a transient thioester-linked intermediate. The transient thioester-linked intermediate then spontaneously undergoes a rearrangement to provide the full length ligation product having a native peptide bond at the ligation site. Full length ligation products are chemically identical to proteins produced by cell free synthesis. Full length ligation products may be refolded and/or oxidized, as allowed, to form native disulfide-containing protein molecules. (see e.g., U.S. Patent Nos. 6,184,344 and 6,174,530; and T. W. Muir et al., *Curr. Opin. Biotech.* (1993): vol. 4, p 420; M. Miller, et al., *Science* (1989): vol. 246, p 1149; A. Wlodawer, et al., *Science* (1989): vol. 245, p 616; L. H. Huang, et al., *Biochemistry* (1991): vol. 30, p 7402; M. Schnolzer, et al., *Int. J. Pept. Prot. Res.* (1992): vol. 40, p 180-193; K. Rajarathnam, et al., *Science* (1994): vol. 264, p 90; R. E. Offord, "Chemical Approaches to Protein Engineering", in *Protein Design and the Development of New therapeutics and Vaccines*, J. B. Hook, G. Poste, Eds., (Plenum Press, New York, 1990) pp. 253-282; C. J. A. Wallace, et al., *J. Biol. Chem.* (1992): vol. 267, p 3852; L. Abrahmsen, et al., *Biochemistry* (1991): vol. 30, p 4151; T. K. Chang, et al., *Proc. Natl. Acad. Sci. USA* (1994) 91: 12544-12548; M. Schnlzer, et al., *Science* (1992): vol., 3256, p 221; and K. Akaji, et al., *Chem. Pharm. Bull. (Tokyo)* (1985) 33: 184).

In certain embodiments, it may be advantageous to provide naturally-occurring or experimentally-derived homologs of a polypeptide of the invention. Such homologs may function in a limited capacity as a modulator to promote or inhibit a subset of the biological activities of the naturally-occurring form of the polypeptide. Thus, specific biological effects may be elicited by treatment with a homolog of limited function, and with fewer side effects relative to treatment with agonists or antagonists which are directed to all of the biological activities of a polypeptide of the invention. For instance, antagonistic homologs may be generated which interfere with the ability of the wild-type polypeptide of the invention to associate with certain proteins, but which do not substantially interfere with the formation of complexes between the native polypeptide and other cellular proteins.

Another aspect of the invention relates to polypeptides derived from the full-length polypeptides of the invention. Isolated peptidyl portions of those polypeptides may be

obtained by screening polypeptides recombinantly produced from the corresponding fragment of the nucleic acid encoding such polypeptides. In addition, fragments may be chemically synthesized using techniques known in the art such as conventional Merrifield solid phase f-Moc or t-Boc chemistry. For example, proteins may be arbitrarily divided
5 into fragments of desired length with no overlap of the fragments, or may be divided into overlapping fragments of a desired length. The fragments may be produced (recombinantly or by chemical synthesis) and tested to identify those peptidyl fragments having a desired property, for example, the capability of functioning as a modulator of the polypeptides of the invention. In an illustrative embodiment, peptidyl portions of a protein of the invention
10 may be tested for binding activity, as well as inhibitory ability, by expression as, for example, thioredoxin fusion proteins, each of which contains a discrete fragment of a protein of the invention (see, for example, U.S. Patents 5,270,181 and 5,292,646; and PCT publication WO94/ 02502).

In another embodiment, truncated polypeptides may be prepared. Truncated
15 polypeptides have from 1 to 20 or more amino acid residues removed from either or both the N- and C-termini. Such truncated polypeptides may prove more amenable to expression, purification or characterization than the full-length polypeptide. For example, truncated polypeptides may prove more amenable than the full-length polypeptide to crystallization, to yielding high quality diffracting crystals or to yielding an HSQC
20 spectrum with high intensity peaks and minimally overlapping peaks. In addition, the use of truncated polypeptides may also identify stable and active domains of the full-length polypeptide that may be more amenable to characterization.

It is also possible to modify the structure of the polypeptides of the invention for such purposes as enhancing therapeutic or prophylactic efficacy, or stability (e.g., *ex vivo*
25 shelf life, resistance to proteolytic degradation *in vivo*, etc.). Such modified polypeptides, when designed to retain at least one activity of the naturally-occurring form of the protein, are considered "functional equivalents" of the polypeptides described in more detail herein. Such modified polypeptides may be produced, for instance, by amino acid substitution, deletion, or addition, which substitutions may consist in whole or part by conservative
30 amino acid substitutions.

For instance, it is reasonable to expect that an isolated conservative amino acid substitution, such as replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, will not have a major affect on the biological activity

of the resulting molecule. Whether a change in the amino acid sequence of a polypeptide results in a functional homolog may be readily determined by assessing the ability of the variant polypeptide to produce a response similar to that of the wild-type protein. Polypeptides in which more than one replacement has taken place may readily be tested in the same manner.

This invention further contemplates a method of generating sets of combinatorial mutants of polypeptides of the invention, as well as truncation mutants, and is especially useful for identifying potential variant sequences (e.g. homologs). The purpose of screening such combinatorial libraries is to generate, for example, homologs which may modulate the activity of a polypeptide of the invention, or alternatively, which possess novel activities altogether. Combinatorially-derived homologs may be generated which have a selective potency relative to a naturally-occurring protein. Such homologs may be used in the development of therapeutics.

Likewise, mutagenesis may give rise to homologs which have intracellular half-lives dramatically different than the corresponding wild-type protein. For example, the altered protein may be rendered either more stable or less stable to proteolytic degradation or other cellular process which result in destruction of, or otherwise inactivation of the protein. Such homologs, and the genes which encode them, may be utilized to alter protein expression by modulating the half-life of the protein. As above, such proteins may be used for the development of therapeutics or treatment.

In similar fashion, protein homologs may be generated by the present combinatorial approach to act as antagonists, in that they are able to interfere with the activity of the corresponding wild-type protein.

In a representative embodiment of this method, the amino acid sequences for a population of protein homologs are aligned, preferably to promote the highest homology possible. Such a population of variants may include, for example, homologs from one or more species, or homologs from the same species but which differ due to mutation. Amino acids which appear at each position of the aligned sequences are selected to create a degenerate set of combinatorial sequences. In certain embodiments, the combinatorial library is produced by way of a degenerate library of genes encoding a library of polypeptides which each include at least a portion of potential protein sequences. For instance, a mixture of synthetic oligonucleotides may be enzymatically ligated into gene sequences such that the degenerate set of potential nucleotide sequences are expressible as

individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g. for phage display).

There are many ways by which the library of potential homologs may be generated from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene
5 sequence may be carried out in an automatic DNA synthesizer, and the synthetic genes may then be ligated into an appropriate vector for expression. One purpose of a degenerate set of genes is to provide, in one mixture, all of the sequences encoding the desired set of potential protein sequences. The synthesis of degenerate oligonucleotides is well known in the art (see for example, Narang, SA (1983) *Tetrahedron* 39:3; Itakura et al., (1981)
10 *Recombinant DNA, Proc. 3rd Cleveland Sympos. Macromolecules*, ed. AG Walton, Amsterdam: Elsevier pp. 273-289; Itakura et al., (1984) *Annu. Rev. Biochem.* 53:323; Itakura et al., (1984) *Science* 198:1056; Ike et al., (1983) *Nucleic Acid Res.* 11:477). Such techniques have been employed in the directed evolution of other proteins (see, for example, Scott et al., (1990) *Science* 249:386-390; Roberts et al., (1992) *PNAS USA*
15 89:2429-2433; Devlin et al., (1990) *Science* 249: 404-406; Cwirla et al., (1990) *PNAS USA* 87: 6378-6382; as well as U.S. Patent Nos: 5,223,409, 5,198,346, and 5,096,815).

Alternatively, other forms of mutagenesis may be utilized to generate a combinatorial library. For example, protein homologs (both agonist and antagonist forms) may be generated and isolated from a library by screening using, for example, alanine
20 scanning mutagenesis and the like (Ruf et al., (1994) *Biochemistry* 33:1565-1572; Wang et al., (1994) *J. Biol. Chem.* 269:3095-3099; Balint et al., (1993) *Gene* 137:109-118; Grodberg et al., (1993) *Eur. J. Biochem.* 218:597-601; Nagashima et al., (1993) *J. Biol. Chem.* 268:2888-2892; Lowman et al., (1991) *Biochemistry* 30:10832-10838; and Cunningham et al., (1989) *Science* 244:1081-1085), by linker scanning mutagenesis (Gustin et al., (1993)
25 *Virology* 193:653-660; Brown et al., (1992) *Mol. Cell Biol.* 12:2644-2652; McKnight et al., (1982) *Science* 232:316); by saturation mutagenesis (Meyers et al., (1986) *Science* 232:613); by PCR mutagenesis (Leung et al., (1989) *Method Cell Mol Biol* 1:11-19); or by random mutagenesis (Miller et al., (1992) *A Short Course in Bacterial Genetics*, CSHL Press, Cold Spring Harbor, NY; and Greener et al., (1994) *Strategies in Mol Biol* 7:32-34).
30 Linker scanning mutagenesis, particularly in a combinatorial setting, is an attractive method for identifying truncated forms of proteins that are bioactive.

A wide range of techniques are known in the art for screening gene products of combinatorial libraries made by point mutations and truncations, and for screening cDNA

libraries for gene products having a certain property. Such techniques will be generally adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of protein homologs. The most widely used techniques for screening large gene libraries typically comprises cloning the gene library into replicable expression
5 vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates relatively easy isolation of the vector encoding the gene whose product was detected. Each of the illustrative assays described below are amenable to high throughput analysis as necessary to screen large numbers of degenerate sequences created by combinatorial
10 mutagenesis techniques.

In an illustrative embodiment of a screening assay, candidate combinatorial gene products are displayed on the surface of a cell and the ability of particular cells or viral particles to bind to the combinatorial gene product is detected in a "panning assay". For instance, the gene library may be cloned into the gene for a surface membrane protein of a
15 bacterial cell (Ladner et al., WO 88/06630; Fuchs et al., (1991) *Bio/Technology* 9:1370-1371; and Goward et al., (1992) *TIBS* 18:136-140), and the resulting fusion protein detected by panning, e.g. using a fluorescently labeled molecule which binds the cell surface protein, e.g. FITC-substrate, to score for potentially functional homologs. Cells may be visually inspected and separated under a fluorescence microscope, or, when the morphology of the
20 cell permits, separated by a fluorescence-activated cell sorter. This method may be used to identify substrates or other polypeptides that can interact with a polypeptide of the invention.

In similar fashion, the gene library may be expressed as a fusion protein on the surface of a viral particle. For instance, in the filamentous phage system, foreign peptide
25 sequences may be expressed on the surface of infectious phage, thereby conferring two benefits. First, because these phage may be applied to affinity matrices at very high concentrations, a large number of phage may be screened at one time. Second, because each infectious phage displays the combinatorial gene product on its surface, if a particular phage is recovered from an affinity matrix in low yield, the phage may be amplified by
30 another round of infection. The group of almost identical *E. coli* filamentous phages M13, fd, and f1 are most often used in phage display libraries, as either of the phage gIII or gVIII coat proteins may be used to generate fusion proteins without disrupting the ultimate packaging of the viral particle (Ladner et al., PCT publication WO 90/02909; Garrard et al.,

PCT publication WO 92/09690; Marks et al., (1992) *J. Biol. Chem.* 267:16007-16010; Griffiths et al., (1993) *EMBO J.* 12:725-734; Clackson et al., (1991) *Nature* 352:624-628; and Barbas et al., (1992) *PNAS USA* 89:4457-4461). Other phage coat proteins may be used as appropriate.

5 The invention also provides for reduction of the polypeptides of the invention to generate mimetics, e.g. peptide or non-peptide agents, which are able to mimic binding of the authentic protein to another cellular partner. Such mutagenic techniques as described above, as well as the thioredoxin system, are also particularly useful for mapping the determinants of a protein which participates in a protein-protein interaction with another
10 protein. To illustrate, the critical residues of a protein which are involved in molecular recognition of a substrate protein may be determined and used to generate peptidomimetics that may bind to the substrate protein. The peptidomimetic may then be used as an inhibitor of the wild-type protein by binding to the substrate and covering up the critical residues needed for interaction with the wild-type protein, thereby preventing interaction of
15 the protein and the substrate. By employing, for example, scanning mutagenesis to map the amino acid residues of a protein which are involved in binding a substrate polypeptide, peptidomimetic compounds may be generated which mimic those residues in binding to the substrate. For instance, non-hydrolyzable peptide analogs of such residues may be generated using benzodiazepine (e.g., see Freidinger et al., in *Peptides: Chemistry and*
20 *Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), azepine (e.g., see Huffman et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), substituted gamma lactam rings (Garvey et al., in *Peptides: Chemistry and Biology*, G.R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), keto-methylene pseudopeptides (Ewenson et al., (1986) *J. Med. Chem.*
25 29:295; and Ewenson et al., in *Peptides: Structure and Function* (Proceedings of the 9th American Peptide Symposium) Pierce Chemical Co. Rockland, IL, 1985), β -turn dipeptide cores (Nagai et al., (1985) *Tetrahedron Lett* 26:647; and Sato et al., (1986) *J Chem Soc Perkin Trans* 1:1231), and β -aminoalcohols (Gordon et al., (1985) *Biochem Biophys Res Commun* 126:419; and Dann et al., (1986) *Biochem Biophys Res Commun* 134:71).

30 The activity of a polypeptide of the invention may be identified and/or assayed using a variety of methods well known to the skilled artisan. For example, information about the activity of non-essential genes may be assayed by creating a null mutant strain of bacteria expressing a mutant form of, or lacking expression of, a protein of interest. The

resulting phenotype of the null mutant strain may provide information about the activity of the mutated gene product. Essential genes may be studied by creating a bacterial strain with a conditional mutation in the gene of interest. The bacterial strain may be grown under permissive and non-permissive conditions and the change in phenotype under the
5 non-permissive conditions may be used to identify and/or assay the activity of the gene product.

In an alternative embodiment, the activity of a protein may be assayed using an appropriate substrate or binding partner or other reagent suitable to test for the suspected activity. For catalytic activity, the assay is typically designed so that the enzymatic reaction
10 produces a detectable signal. For example, mixture of a kinase with a substrate in the presence of ^{32}P will result in incorporation of the ^{32}P into the substrate. The labeled substrate may then be separated from the free ^{32}P and the presence and/or amount of radiolabeled substrate may be detected using a scintillation counter or a phosphorimager. Similar assays may be designed to identify and/or assay the activity of a wide variety of
15 enzymatic activities. Based on the teachings herein, the skilled artisan would readily be able to develop an appropriate assay for a polypeptide of the invention.

In another embodiment, the activity of a polypeptide of the invention may be determined by assaying for the level of expression of RNA and/or protein molecules. Transcription levels may be determined, for example, using Northern blots, hybridization to
20 an oligonucleotide array or by assaying for the level of a resulting protein product. Translation levels may be determined, for example, using Western blotting or by identifying a detectable signal produced by a protein product (e.g., fluorescence, luminescence, enzymatic activity, etc.). Depending on the particular situation, it may be desirable to detect the level of transcription and/or translation of a single gene or of
25 multiple genes.

Alternatively, it may be desirable to measure the overall rate of DNA replication, transcription and/or translation in a cell. In general this may be accomplished by growing the cell in the presence of a detectable metabolite which is incorporated into the resultant DNA, RNA, or protein product. For example, the rate of DNA synthesis may be
30 determined by growing cells in the presence of BrdU which is incorporated into the newly synthesized DNA. The amount of BrdU may then be determined histochemically using an anti-BrdU antibody.

In general, the biological activity of a polypeptide encoded by SEQ ID NO. 2, and possibly other polypeptides of the invention, is expected to be characterized as having a biochemical activity substantially similar to that of histidine tRNA synthetase, having the gene designation of *hisS*, although the target specificity and/or other biological context for the biological activity of a polypeptide of the invention may be somewhat different from that protein. An alternate gene designation for histidine tRNA synthetase is *Syh*. The foregoing annotations were determined in accordance with the procedure described in EXAMPLE 17. This functionality assignment has been confirmed by completion of the X-ray structure of a polypeptide of the invention, as described in more detail below. In one aspect, the present invention contemplates a polypeptide having biological activity, or is a component of a protein complex having biological activity, substantially similar to or identical to histidine tRNA synthetase. Alternatively, the polypeptide catalyzes, or is a component of a protein complex that catalyzes, a reaction that is substantially the same type of, or is the same as, the reaction catalyzed by histidine tRNA synthetase. Other biological activities of polypeptides of the invention are described herein, or will be reasonably apparent to those skilled in the art in light of the present disclosure.

The enzymes involved in aminoacyl-tRNA (AA-tRNA) synthesis, a process substantially responsible for the accuracy of protein synthesis, are believed to be highly species-specific. In particular, a number of pathogens contain certain pathways of AA-tRNA synthesis that are unrelated to those found in their mammalian hosts. Since AA-tRNA synthesis is believed to be required for cell viability, the discovery of pathogen-specific pathways and enzymes, including the polypeptides of the present invention, presents novel therapeutic and diagnostic targets. Such enzymes are reported as being the targets of several known drugs. Some microorganisms, however, are resistance to such drugs, for example, some strains of *Streptococcus pneumoniae* have been reported as having varying resistance to the drug mupirocin.

Aminoacyl-tRNA synthetases (AARS) is thought to catalyze the first step in protein synthesis by the formation of aminoacyl adenylate (AA-AMP) and to transfer it onto tRNA to form charged tRNA to allow protein synthesis to proceed. In these reactions, an amino acid is associated with a specific nucleotide triplet of the genetic code by virtue of being linked to a specific tRNA that harbors the anticodon triplet cognate to the amino acid. Most organisms make twenty different aminoacyl-tRNA synthetases, one for each type of amino acid. These twenty enzymes are known to be widely different, each optimized for function

with its own particular amino acid and the set of tRNA molecules appropriate to that amino acid. It is necessary that aminoacyl-tRNA synthetases perform their tasks with high accuracy, for each mistake they make will result in a misplaced amino acid when new proteins are constructed. It has been observed that such enzymes make about one mistake
5 in 10,000. Aminoacyl-tRNA synthetases are essential proteins found in all living organisms. They form a diverse group of enzymes that ensure the fidelity of transfer of genetic information from the DNA into the protein.

Histidyl-tRNA synthetase (HisRS or Syh), which has been observed to catalyze the charging of histidine onto its cognate tRNA His, is a homo-dimer of about 95 kDa.
10 Histidine is one of the most critical amino acids in proteins, found often as a catalytic residue or a ligand for metals. A high degree of accuracy for charging tRNA^{His} with the correct amino acid is very important. HisRS is a class II aminoacyl-tRNA synthetase, and has been further grouped into subclass IIa, along with seryl-, prolyl-, threonyl-, and some glycyl-tRNA synthetases on the basis of sequence similarities in the C-terminal anticodon-binding domain. However, it is distinct from other class IIa synthetases in that HisRS has
15 two additional motifs, histidine A (HisA, RGLDYY) and histidine B (HisB, GGRYDG), both of which are conserved among all known HisRS.

There are several postulated mechanisms for improving charging fidelity of the tRNA synthetases. One of them uses a preformed and well-defined amino acid binding
20 pocket. For example, TyrRS has a pocket that appears to provide sufficient affinity differences to discriminate between tyrosine and the closely related phenylalanine and GlnRS appears to use additional elements from tRNA to establish the amino acid binding pocket. IleRS illustrates another mechanism, in which the rigid amino acid binding site is thought not to provide enough discrimination against valine. Therefore, a hydrolytic editing
25 domain is thought to have evolved to correct these errors in IleRS. The dynamic HisA motif found when comparing the apo and holo structures in HisRS offers a third novel fidelity mechanism. Although substrate binding and catalysis require some degree of cooperative dynamics in other synthetases, the large-scale cooperative dynamics proposed for HisRS may have evolved for charging fidelity as well as efficient product release.

30 Histidine-specific tRNAs are thought to be unique due to the additional guanosine (designated G-1) present at their 5' end, giving rise through pairing with the discriminator base (C73 in prokaryotes and organelles, A73 or G73 in eukaryotes) to an extra base pair in the acceptor stem. From the results of *in vitro* transcript amino-acylation experiments, the

G-1, C73 base pair in *E. coli* is thought to be the most important determinant for HisRS. Furthermore, mini helices corresponding to the acceptor stem and loop of tRNA^{His} have been observed to be efficiently amino-acylated by HisRS. More recently, *in vivo* studies have indicated that the identity of histidine tRNAs in *E. coli* depends more on C73 than G-1. On the other hand, in the yeast histidyl system, the exact nature of the additional base pair seems less important (except that G73 is a strong negative determinant), suggesting that the major recognition elements may be the extra backbone groups at the 5' end. For specific recognition of the GUG anti-codon, *in vitro* results suggest that in the *E. coli* system the anticodon bases are weak identity elements, whereas in the yeast system bases 34 and 35, but not 36, are relatively more important. The manner of binding of the C-terminal domain of class IIa synthetases to the anticodon stem-loop is one of the remaining open structural questions about this subclass of synthetases.

For all of the foregoing reasons, the polypeptides of the present invention are potentially valuable targets for therapeutics and diagnostics.

15

3. Nucleic Acids of the Invention

One aspect of the invention pertains to isolated nucleic acids of the invention. For example, the present invention contemplates an isolated nucleic acid comprising (a) the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, (b) a nucleotide sequence at least 80% identical to SEQ ID NO: 1 or SEQ ID NO: 3, (c) a nucleotide sequence that hybridizes under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3, or (d) the complement of the nucleotide sequence of (a), (b) or (c). In certain embodiments, nucleic acids of the invention may be labeled, with for example, a radioactive, chemiluminescent or fluorescent label.

It may be that case that the nucleic acid sequence of SEQ ID NO: 3 differs from that of SEQ ID NO: 1 by one or more nucleic acid residues. SEQ ID NO: 3 is determined experimentally, and SEQ ID NO: 1 obtained as described in EXAMPLE 1. In such a case, the present invention contemplates the specific nucleic acid sequences of SEQ ID NO: 1 and SEQ ID NO: 3, and variants thereof, as well as any differences in the applicable amino acid sequences encoded thereby.

In another aspect, the present invention contemplates an isolated nucleic acid that specifically hybridizes under stringent conditions to at least ten nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof, which nucleic acid can specifically detect

or amplify SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof. In yet another aspect, the present invention contemplates such an isolated nucleic acid comprising a nucleotide sequence encoding a fragment of SEQ ID NO: 2 or SEQ ID NO: 4 at least 8 residues in length. The present invention further contemplates a method of hybridizing an oligonucleotide with a nucleic acid of the invention comprising: (a) providing a single-stranded oligonucleotide at least eight nucleotides in length, the oligonucleotide being complementary to a portion of a nucleic acid of the invention; and (b) contacting the oligonucleotide with a sample comprising a nucleic acid of the acid under conditions that permit hybridization of the oligonucleotide with the nucleic acid of the invention.

Isolated nucleic acids which differ from the nucleic acids of the invention due to degeneracy in the genetic code are also within the scope of the invention. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC are synonyms for histidine) may result in "silent" mutations which do not affect the amino acid sequence of the protein. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the polypeptides of the invention will exist. One skilled in the art will appreciate that these variations in one or more nucleotides (from less than 1% up to about 3 or 5% or possibly more of the nucleotides) of the nucleic acids encoding a particular protein of the invention may exist among a given species due to natural allelic variation. Any and all such nucleotide variations and resulting amino acid polymorphisms are within the scope of this invention.

Bias in codon choice within genes in a single species appears related to the level of expression of the protein encoded by that gene. Accordingly, the invention encompasses nucleic acid sequences which have been optimized for improved expression in a host cell by altering the frequency of codon usage in the nucleic acid sequence to approach the frequency of preferred codon usage of the host cell. Due to codon degeneracy, it is possible to optimize the nucleotide sequence without affecting the amino acid sequence of an encoded polypeptide. Accordingly, the instant invention relates to any nucleotide sequence that encodes all or a substantial portion of the amino acid sequence set forth in SEQ ID NO: 2, SEQ ID NO: 4 or other polypeptides of the invention.

The present invention pertains to nucleic acids encoding proteins derived from *E. faecalis* and which have amino acid sequences evolutionarily related to a polypeptide of the invention, wherein "evolutionarily related to", refers to proteins having different amino acid

sequences which have arisen naturally (e.g. by allelic variance or by differential splicing), as well as mutational variants of the proteins of the invention which are derived, for example, by combinatorial mutagenesis.

5 Fragments of the polynucleotides of the invention encoding a biologically active portion of the subject polypeptides are also within the scope of the invention. As used herein, a fragment of a nucleic acid of the invention encoding an active portion of a polypeptide of the invention refers to a nucleotide sequence having fewer nucleotides than the nucleotide sequence encoding the full length amino acid sequence of a polypeptide of the invention, for example, SEQ ID NO: 2 or SEQ ID NO: 4, and which encodes a
10 polypeptide which retains at least a portion of a biological activity of the full-length protein as defined herein, or alternatively, which is functional as a modulator of the biological activity of the full-length protein. For example, such fragments include a polypeptide containing a domain of the full-length protein from which the polypeptide is derived that mediates the interaction of the protein with another molecule (e.g., polypeptide, DNA,
15 RNA, etc.). In another embodiment, the present invention contemplates an isolated nucleic acid that encodes a polypeptide having a biological activity of a protein having the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, or alternatively biological activity of histidine tRNA synthetase.

Nucleic acids within the scope of the invention may also contain linker sequences,
20 modified restriction endonuclease sites and other sequences useful for molecular cloning, expression or purification of such recombinant polypeptides.

A nucleic acid encoding a polypeptide of the invention may be obtained from mRNA or genomic DNA from any organism in accordance with protocols described herein, as well as those generally known to those skilled in the art. A cDNA encoding a
25 polypeptide of the invention, for example, may be obtained by isolating total mRNA from an organism, e.g. a bacteria, virus, mammal, etc. Double stranded cDNAs may then be prepared from the total mRNA, and subsequently inserted into a suitable plasmid or bacteriophage vector using any one of a number of known techniques. A gene encoding a polypeptide of the invention may also be cloned using established polymerase chain
30 reaction techniques in accordance with the nucleotide sequence information provided by the invention. In one aspect, the present invention contemplates a method for amplification of a nucleic acid of the invention, or a fragment thereof, comprising: (a) providing a pair of single stranded oligonucleotides, each of which is at least eight nucleotides in length,

complementary to sequences of a nucleic acid of the invention, and wherein the sequences to which the oligonucleotides are complementary are at least ten nucleotides apart; and (b) contacting the oligonucleotides with a sample comprising a nucleic acid comprising the nucleic acid of the invention under conditions which permit amplification of the region
5 located between the pair of oligonucleotides, thereby amplifying the nucleic acid.

Another aspect of the invention relates to the use of nucleic acids of the invention in "antisense therapy". As used herein, antisense therapy refers to administration or *in situ* generation of oligonucleotide probes or their derivatives which specifically hybridize or otherwise bind under cellular conditions with the cellular mRNA and/or genomic DNA
10 encoding one of the polypeptides of the invention so as to inhibit expression of that polypeptide, e.g. by inhibiting transcription and/or translation. The binding may be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interactions in the major groove of the double helix. In general, antisense therapy refers to the range of techniques generally employed in the art, and
15 includes any therapy which relies on specific binding to oligonucleotide sequences.

An antisense construct of the present invention may be delivered, for example, as an expression plasmid which, when transcribed in the cell, produces RNA which is complementary to at least a unique portion of the mRNA which encodes a polypeptide of the invention. Alternatively, the antisense construct may be an oligonucleotide probe which
20 is generated *ex vivo* and which, when introduced into the cell causes inhibition of expression by hybridizing with the mRNA and/or genomic sequences encoding a polypeptide of the invention. Such oligonucleotide probes may be modified oligonucleotides which are resistant to endogenous nucleases, e.g. exonucleases and/or endonucleases, and are therefore stable *in vivo*. Exemplary nucleic acid molecules for use
25 as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patents 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy have been reviewed, for example, by van der Krol et al., (1988) *Biotechniques* 6:958-976; and Stein et al., (1988) *Cancer Res* 48:2659-2668.

30 In a further aspect, the invention provides double stranded small interfering RNAs (siRNAs), and methods for administering the same. siRNAs decrease or block gene expression. While not wishing to be bound by theory, it is generally thought that siRNAs inhibit gene expression by mediating sequence specific mRNA degradation. RNA

interference (RNAi) is the process of sequence-specific, post-transcriptional gene silencing, particularly in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene (Elbashir et al. Nature 2001; 411(6836): 494-8). Accordingly, it is understood that siRNAs and long dsRNAs having substantial
5 sequence identity to all or a portion of SEQ ID NO: 1 or SEQ ID NO: 3 may be used to inhibit the expression of a nucleic acid of the invention, and particularly when the polynucleotide is expressed in a mammalian or plant cell.

The nucleic acids of the invention may be used as diagnostic reagents to detect the presence or absence of the target DNA or RNA sequences to which they specifically bind,
10 such as for determining the level of expression of a nucleic acid of the invention. In one aspect, the present invention contemplates a method for detecting the presence of a nucleic acid of the invention or a portion thereof in a sample, the method comprising: (a) providing an oligonucleotide at least eight nucleotides in length, the oligonucleotide being complementary to a portion of a nucleic acid of the invention; (b) contacting the
15 oligonucleotide with a sample comprising at least one nucleic acid under conditions that permit hybridization of the oligonucleotide with a nucleic acid comprising a nucleotide sequence complementary thereto; and (c) detecting hybridization of the oligonucleotide to a nucleic acid in the sample, thereby detecting the presence of a nucleic acid of the invention or a portion thereof in the sample. In another aspect, the present invention contemplates a
20 method for detecting the presence of a nucleic acid of the invention or a portion thereof in a sample, the method comprising: (a) providing a pair of single stranded oligonucleotides, each of which is at least eight nucleotides in length, complementary to sequences of a nucleic acid of the invention, and wherein the sequences to which the oligonucleotides are complementary are at least ten nucleotides apart; and (b) contacting the oligonucleotides
25 with a sample comprising at least one nucleic acid under hybridization conditions; (c) amplifying the nucleotide sequence between the two oligonucleotide primers; and (d) detecting the presence of the amplified sequence, thereby detecting the presence of a nucleic acid comprising the nucleic acid of the invention or a portion thereof in the sample.

In another aspect of the invention, the subject nucleic acid is provided in an
30 expression vector comprising a nucleotide sequence encoding a polypeptide of the invention and operably linked to at least one regulatory sequence. It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed. The vector's

copy number, the ability to control that copy number and the expression of any other protein encoded by the vector, such as antibiotic markers, should be considered.

The subject nucleic acids may be used to cause expression and over-expression of a polypeptide of the invention in cells propagated in culture, e.g. to produce proteins or polypeptides, including fusion proteins or polypeptides.

This invention pertains to a host cell transfected with a recombinant gene in order to express a polypeptide of the invention. The host cell may be any prokaryotic or eukaryotic cell. For example, a polypeptide of the invention may be expressed in bacterial cells, such as *E. coli*, insect cells (baculovirus), yeast, or mammalian cells. In those instances when the host cell is human, it may or may not be in a live subject. Other suitable host cells are known to those skilled in the art. Additionally, the host cell may be supplemented with tRNA molecules not typically found in the host so as to optimize expression of the polypeptide. Other methods suitable for maximizing expression of the polypeptide will be known to those in the art.

The present invention further pertains to methods of producing the polypeptides of the invention. For example, a host cell transfected with an expression vector encoding a polypeptide of the invention may be cultured under appropriate conditions to allow expression of the polypeptide to occur. The polypeptide may be secreted and isolated from a mixture of cells and medium containing the polypeptide. Alternatively, the polypeptide may be retained cytoplasmically and the cells harvested, lysed and the protein isolated.

A cell culture includes host cells, media and other byproducts. Suitable media for cell culture are well known in the art. The polypeptide may be isolated from cell culture medium, host cells, or both using techniques known in the art for purifying proteins, including ion-exchange chromatography, gel filtration chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies specific for particular epitopes of a polypeptide of the invention.

Thus, a nucleotide sequence encoding all or a selected portion of polypeptide of the invention, may be used to produce a recombinant form of the protein via microbial or eukaryotic cellular processes. Ligating the sequence into a polynucleotide construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures. Similar procedures, or modifications thereof, may be employed to prepare recombinant polypeptides of the invention by microbial means or tissue-culture technology.

Expression vehicles for production of a recombinant protein include plasmids and other vectors. For instance, suitable vectors for the expression of a polypeptide of the invention include plasmids of the types: pBR322-derived plasmids, pEMBL-derived plasmids, pEX-derived plasmids, pBTac-derived plasmids and pUC-derived plasmids for
5 expression in prokaryotic cells, such as *E. coli*.

A number of vectors exist for the expression of recombinant proteins in yeast. For instance, YEP24, YIP5, YEP51, YEP52, pYES2, and YRP17 are cloning and expression vehicles useful in the introduction of genetic constructs into *S. cerevisiae* (see, for example, Broach et al., (1983) in *Experimental Manipulation of Gene Expression*, ed. M. Inouye
10 Academic Press, p. 83). These vectors may replicate in *E. coli* due the presence of the pBR322 ori, and in *S. cerevisiae* due to the replication determinant of the yeast 2 micron plasmid. In addition, drug resistance markers such as ampicillin may be used.

In certain embodiments, mammalian expression vectors contain both prokaryotic sequences to facilitate the propagation of the vector in bacteria, and one or more eukaryotic
15 transcription units that are expressed in eukaryotic cells. The pcDNAI/amp, pcDNAI/neo, pRc/CMV, pSV2gpt, pSV2neo, pSV2-dhfr, pTk2, pRSVneo, pMSG, pSVT7, pko-neo and pHyg derived vectors are examples of mammalian expression vectors suitable for transfection of eukaryotic cells. Some of these vectors are modified with sequences from bacterial plasmids, such as pBR322, to facilitate replication and drug resistance selection in
20 both prokaryotic and eukaryotic cells. Alternatively, derivatives of viruses such as the bovine papilloma virus (BPV-1), or Epstein-Barr virus (pHEBo, pREP-derived and p205) can be used for transient expression of proteins in eukaryotic cells. The various methods employed in the preparation of the plasmids and transformation of host organisms are well known in the art. For other suitable expression systems for both prokaryotic and eukaryotic
25 cells, as well as general recombinant procedures, see *Molecular Cloning A Laboratory Manual*, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press, 1989) Chapters 16 and 17. In some instances, it may be desirable to express the recombinant protein by the use of a baculovirus expression system. Examples of such baculovirus expression systems include pVL-derived vectors (such as pVL1392, pVL1393
30 and pVL941), pAcUW-derived vectors (such as pAcUW1), and pBlueBac-derived vectors (such as the β -gal containing pBlueBac III).

In another variation, protein production may be achieved using *in vitro* translation systems. *In vitro* translation systems are, generally, a translation system which is a cell-free

extract containing at least the minimum elements necessary for translation of an RNA molecule into a protein. An *in vitro* translation system typically comprises at least ribosomes, tRNAs, initiator methionyl-tRNA^{Met}, proteins or complexes involved in translation, e.g., eIF2, eIF3, the cap-binding (CB) complex, comprising the cap-binding protein (CBP) and eukaryotic initiation factor 4F (eIF4F). A variety of *in vitro* translation systems are well known in the art and include commercially available kits. Examples of *in vitro* translation systems include eukaryotic lysates, such as rabbit reticulocyte lysates, rabbit oocyte lysates, human cell lysates, insect cell lysates and wheat germ extracts. Lysates are commercially available from manufacturers such as Promega Corp., Madison, Wis.; Stratagene, La Jolla, Calif.; Amersham, Arlington Heights, Ill.; and GIBCO/BRL, Grand Island, N.Y. *In vitro* translation systems typically comprise macromolecules, such as enzymes, translation, initiation and elongation factors, chemical reagents, and ribosomes. In addition, an *in vitro* transcription system may be used. Such systems typically comprise at least an RNA polymerase holoenzyme, ribonucleotides and any necessary transcription initiation, elongation and termination factors. *In vitro* transcription and translation may be coupled in a one-pot reaction to produce proteins from one or more isolated DNAs.

When expression of a carboxy terminal fragment of a polypeptide is desired, i.e. a truncation mutant, it may be necessary to add a start codon (ATG) to the oligonucleotide fragment containing the desired sequence to be expressed. It is well known in the art that a methionine at the N-terminal position may be enzymatically cleaved by the use of the enzyme methionine aminopeptidase (MAP). MAP has been cloned from *E. coli* (Ben-Bassat et al., (1987) *J. Bacteriol.* 169:751-757) and *Salmonella typhimurium* and its *in vitro* activity has been demonstrated on recombinant proteins (Miller et al., (1987) *PNAS USA* 84:2718-1722). Therefore, removal of an N-terminal methionine, if desired, may be achieved either *in vivo* by expressing such recombinant polypeptides in a host which produces MAP (e.g., *E. coli* or CM89 or *S. cerevisiae*), or *in vitro* by use of purified MAP (e.g., procedure of Miller et al.).

Coding sequences for a polypeptide of interest may be incorporated as a part of a fusion gene including a nucleotide sequence encoding a different polypeptide. The present invention contemplates an isolated nucleic acid comprising a nucleic acid of the invention and at least one heterologous sequence encoding a heterologous peptide linked in frame to the nucleotide sequence of the nucleic acid of the invention so as to encode a fusion protein comprising the heterologous polypeptide. The heterologous polypeptide may be fused to

(a) the C-terminus of the polypeptide encoded by the nucleic acid of the invention, (b) the N-terminus of the polypeptide, or (c) the C-terminus and the N-terminus of the polypeptide. In certain instances, the heterologous sequence encodes a polypeptide permitting the detection, isolation, solubilization and/or stabilization of the polypeptide to which it is fused. In still other embodiments, the heterologous sequence encodes a polypeptide selected from the group consisting of a polyHis tag, myc, HA, GST, protein A, protein G, calmodulin-binding peptide, thioredoxin, maltose-binding protein, poly arginine, poly His-Asp, FLAG, a portion of an immunoglobulin protein, and a transcytosis peptide.

Fusion expression systems can be useful when it is desirable to produce an immunogenic fragment of a polypeptide of the invention. For example, the VP6 capsid protein of rotavirus may be used as an immunologic carrier protein for portions of polypeptide, either in the monomeric form or in the form of a viral particle. The nucleic acid sequences corresponding to the portion of a polypeptide of the invention to which antibodies are to be raised may be incorporated into a fusion gene construct which includes coding sequences for a late vaccinia virus structural protein to produce a set of recombinant viruses expressing fusion proteins comprising a portion of the protein as part of the virion. The Hepatitis B surface antigen may also be utilized in this role as well. Similarly, chimeric constructs coding for fusion proteins containing a portion of a polypeptide of the invention and the poliovirus capsid protein may be created to enhance immunogenicity (see, for example, EP Publication NO: 0259149; and Evans et al., (1989) *Nature* 339:385; Huang et al., (1988) *J. Virol.* 62:3855; and Schlienger et al., (1992) *J. Virol.* 66:2).

Fusion proteins may facilitate the expression and/or purification of proteins. For example, a polypeptide of the invention may be generated as a glutathione-S-transferase (GST) fusion protein. Such GST fusion proteins may be used to simplify purification of a polypeptide of the invention, such as through the use of glutathione-derivatized matrices (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al., (N.Y.: John Wiley & Sons, 1991)). In another embodiment, a fusion gene coding for a purification leader sequence, such as a poly-(His)/enterokinase cleavage site sequence at the N-terminus of the desired portion of the recombinant protein, may allow purification of the expressed fusion protein by affinity chromatography using a Ni^{2+} metal resin. The purification leader sequence may then be subsequently removed by treatment with enterokinase to provide the purified protein (e.g., see Hochuli et al., (1987) *J. Chromatography* 411: 177; and Janknecht et al., *PNAS USA* 88:8972).

Techniques for making fusion genes are well known. Essentially, the joining of various DNA fragments coding for different polypeptide sequences is performed in accordance with conventional techniques, employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene may be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments may be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which may subsequently be annealed to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al., John Wiley & Sons: 1992).

The present invention further contemplates a transgenic non-human animal having cells which harbor a transgene comprising a nucleic acid of the invention.

In other embodiments, the invention provides for nucleic acids of the invention immobilized onto a solid surface, including, plates, microtiter plates, slides, beads, particles, spheres, films, strands, precipitates, gels, sheets, tubing, containers, capillaries, pads, slices, etc. The nucleic acids of the invention may be immobilized onto a chip as part of an array. The array may comprise one or more polynucleotides of the invention as described herein. In one embodiment, the chip comprises one or more polynucleotides of the invention as part of an array of *E. faecalis* polynucleotide sequences.

In still other embodiments, the invention comprises the sequence of a nucleic acid of the invention in computer readable format. The invention also encompasses a database comprising the sequence of a nucleic acid of the invention.

4. Homology Searching of Nucleotide and Polypeptide Sequences

The nucleotide or amino acid sequences of the invention, including those set forth in the appended Figures, may be used as query sequences against databases such as GenBank, SwissProt, PDB, BLOCKS, and Pima II. These databases contain previously identified and annotated sequences that may be searched for regions of homology (similarity) using BLAST, which stands for Basic Local Alignment Search Tool (Altschul S F (1993) J Mol Evol 36:290-300; Altschul, S F et al (1990) J Mol Biol 215:403-10).

BLAST produces alignments of both nucleotide and amino acid sequences to determine sequence similarity. Because of the local nature of the alignments, BLAST is

especially useful in determining exact matches or in identifying homologs which may be of prokaryotic (bacterial) or eukaryotic (animal, fungal or plant) origin. Other algorithms such as the one described in Smith, R. F. and T. F. Smith (1992; Protein Engineering 5:35-51) may be used when dealing with primary sequence patterns and secondary structure gap penalties. In the usual course using BLAST, sequences have lengths of at least 49 nucleotides and no more than 12% uncalled bases (where N is recorded rather than A, C, G, or T).

The BLAST approach, as detailed in Karlin and Altschul (1993; Proc Nat Acad Sci 90:5873-7) searches matches between a query sequence and a database sequence, to evaluate the statistical significance of any matches found, and to report only those matches which satisfy the user-selected threshold of significance. The threshold is typically set at about 10-25 for nucleotides and about 3-15 for peptides.

5. Analysis of Protein Properties

15 (a) Analysis of Proteins by Mass Spectrometry

Typically, protein characterization by mass spectroscopy first requires protein isolation followed by either chemical or enzymatic digestion of the protein into smaller peptide fragments, whereupon the peptide fragments may be analyzed by mass spectrometry to obtain a peptide map. Mass spectrometry may also be used to identify post-translational modifications (e.g., phosphorylation, etc.) of a polypeptide.

Various mass spectrometers may be used within the present invention. Representative examples include: triple quadrupole mass spectrometers, magnetic sector instruments (magnetic tandem mass spectrometer, JEOL, Peabody, Mass), ionspray mass spectrometers (Bruins et al., Anal Chem. 59:2642-2647, 1987), electrospray mass spectrometers (including tandem, nano- and nano-electrospray tandem) (Fenn et al., Science 246:64-71, 1989), laser desorption time-of-flight mass spectrometers (Karas and Hillenkamp, Anal. Chem. 60:2299-2301, 1988), and a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (Extrel Corp., Pittsburgh, Mass.).

MALDI ionization is a technique in which samples of interest, in this case peptides and proteins, are co-crystallized with an acidified matrix. The matrix is typically a small molecule that absorbs at a specific wavelength, generally in the ultraviolet (UV) range, and dissipates the absorbed energy thermally. Typically a pulsed laser beam is used to transfer energy rapidly (i.e., a few ns) to the matrix. This transfer of energy causes the matrix to

rapidly dissociate from the MALDI plate surface and results in a plume of matrix and the co-crystallized analytes being transferred into the gas phase. MALDI is considered a "soft-ionization" method that typically results in singly-charged species in the gas phase, most often resulting from a protonation reaction with the matrix. MALDI may be coupled in-line
5 with time of flight (TOF) mass spectrometers. TOF detectors are based on the principle that an analyte moves with a velocity proportional to its mass. Analytes of higher mass move slower than analytes of lower mass and thus reach the detector later than lighter analytes. The present invention contemplates a composition comprising a polypeptide of the invention and a matrix suitable for mass spectrometry. In certain instances, the matrix is a
10 nicotinic acid derivative or a cinnamic acid derivative.

MALDI-TOF MS is easily performed with modern mass spectrometers. Typically the samples of interest, in this case peptides or proteins, are mixed with a matrix and spotted onto a polished stainless steel plate (MALDI plate). Commercially available MALDI plates can presently hold up to 1536 samples per plate. Once spotted with sample,
15 the MALDI sample plate is then introduced into the vacuum chamber of a MALDI mass spectrometer. The pulsed laser is then activated and the mass to charge ratios of the analytes are measured utilizing a time of flight detector. A mass spectrum representing the mass to charge ratios of the peptides/proteins is generated.

As mentioned above, MALDI can be utilized to measure the mass to charge ratios
20 of both proteins and peptides. In the case of proteins, a mixture of intact protein and matrix are co-crystallized on a MALDI target (Karas, M. and Hillenkamp, F. Anal. Chem. 1988, 60 (20) 2299-2301). The spectrum resulting from this analysis is employed to determine the molecular weight of a whole protein. This molecular weight can then be compared to the theoretical weight of the protein and utilized in characterizing the analyte of interest,
25 such as whether or not the protein has undergone post-translational modifications (e.g., example phosphorylation).

In certain embodiments, MALDI mass spectrometry is used for determination of peptide maps of digested proteins. The peptide masses are measured accurately using a MALDI-TOF or a MALDI-Q-Star mass spectrometer, with detection precision down to the
30 low ppm (parts per million) level. The ensemble of the peptide masses observed in a protein digest, such as a tryptic digest, may be used to search protein/DNA databases in a method called peptide mass fingerprinting. In this approach, protein entries in a database are ranked according to the number of experimental peptide masses that match the

predicted trypsin digestion pattern. Commercially available software utilizes a search algorithm that provides a scoring scheme based on the size of the databases, the number of matching peptides, and the different peptides. Depending on the number of peptides observed, the accuracy of the measurement, and the size of the genome of the particular species, unambiguous protein identification may be obtained.

Statistical analysis may be performed upon each protein match to determine the validity of the match. Typical constraints include error tolerances within 0.1 Da for monoisotopic peptide masses, cysteines may be alkylated and searched as carboxyamidomethyl modifications, 0 or 1 missed enzyme cleavages, and no methionine oxidations allowed. Identified proteins may be stored automatically in a relational database with software links to SDS-PAGE images and ligand sequences. Often even a partial peptide map is specific enough for identification of the protein. If no protein match is found, a more error-tolerant search can be used, for example using fewer peptides or allowing a larger margin error with respect to mass accuracy.

Other mass spectroscopy methods such as tandem mass spectrometry or post source decay may be used to obtain sequence information about proteins that cannot be identified by peptide mass mapping, or to confirm the identity of proteins that are tentatively identified by an error-tolerant peptide mass search described above. (Griffin et al, Rapid Commun. Mass. Spectrom. 1995, 9, 1546-51).

(b) Analysis of Proteins by Nuclear Magnetic Resonance (NMR)

NMR may be used to characterize the structure of a polypeptide in accordance with the methods of the invention. In particular, NMR can be used, for example, to determine the three dimensional structure, the conformational state, the aggregation level, the state of protein folding/unfolding or the dynamic properties of a polypeptide. For example, the present invention contemplates a method for determining three dimensional structure information of a polypeptide of the invention, the method comprising: (a) generating a purified isotopically labeled polypeptide of the invention; and (b) subjecting the polypeptide to NMR spectroscopic analysis, thereby determining information about its three dimensional structure.

Interaction between a polypeptide and another molecule can also be monitored using NMR. Thus, the invention encompasses methods for detecting, designing and characterizing interactions between a polypeptide and another molecule, including polypeptides, nucleic acids and small molecules, utilizing NMR techniques. For example,

the present invention contemplates a method for determining three dimensional structure information of a polypeptide of the invention, or a fragment thereof, while the polypeptide is complexed with another molecule, the method comprising: (a) generating a purified isotopically labeled polypeptide of the invention, or a fragment thereof; (b) forming a
5 complex between the polypeptide and the other molecule; and (c) subjecting the complex to NMR spectroscopic analysis, thereby determining information about the three dimensional structure of the polypeptide. In another aspect, the present invention contemplates a method for identifying compounds that bind to a polypeptide of the invention, or a fragment thereof, the method comprising: (a) generating a first NMR spectrum of an isotopically
10 labeled polypeptide of the invention, or a fragment thereof; (b) exposing the polypeptide to one or more chemical compounds; (c) generating a second NMR spectrum of the polypeptide which has been exposed to one or more chemical compounds; and (d) comparing the first and second spectra to determine differences between the first and the second spectra, wherein the differences are indicative of one or more compounds that have
15 bound to the polypeptide.

Briefly, the NMR technique involves placing the material to be examined (usually in a suitable solvent) in a powerful magnetic field and irradiating it with radio frequency (rf) electromagnetic radiation. The nuclei of the various atoms will align themselves with the magnetic field until energized by the rf radiation. They then absorb this resonant energy
20 and re-radiate it at a frequency dependent on i) the type of nucleus and ii) its atomic environment. Moreover, resonant energy may be passed from one nucleus to another, either through bonds or through three-dimensional space, thus giving information about the environment of a particular nucleus and nuclei in its vicinity.

However, it is important to recognize that not all nuclei are NMR active. Indeed,
25 not all isotopes of the same element are active. For example, whereas "ordinary" hydrogen, ^1H , is NMR active, heavy hydrogen (deuterium), ^2H , is not active in the same way. Thus, any material that normally contains ^1H hydrogen may be rendered "invisible" in the hydrogen NMR spectrum by replacing all or almost all the ^1H hydrogens with ^2H . It is for this reason that NMR spectroscopic analyses of water-soluble materials frequently are
30 performed in $^2\text{H}_2\text{O}$ (or deuterium) to eliminate the water signal.

Conversely, "ordinary" carbon, ^{12}C , is NMR inactive whereas the stable isotope, ^{13}C , present to about 1% of total carbon in nature, is active. Similarly, while "ordinary" nitrogen, ^{14}N , is NMR active, it has undesirable properties for NMR and resonates at a

different frequency from the stable isotope ^{15}N , present to about 0.4% of total nitrogen in nature.

By labeling proteins with ^{15}N and $^{15}\text{N}/^{13}\text{C}$, it is possible to conduct analytical NMR of macromolecules with weights of 15 kD and 40 kD, respectively. More recently, partial
5 deuteration of the protein in addition to ^{13}C - and ^{15}N -labeling has increased the possible weight of proteins and protein complexes for NMR analysis still further, to approximately 60-70 kD. See Shan et al., *J. Am. Chem. Soc.*, 118:6570-6579 (1996); L.E. Kay, *Methods Enzymol.*, 339:174-203 (2001); and K.H. Gardner & L.E. Kay, *Annu Rev Biophys Biomol Struct.*, 27:357-406 (1998); and references cited therein.

10 Isotopic substitution may be accomplished by growing a bacterium or yeast or other type of cultured cells, transformed by genetic engineering to produce the protein of choice, in a growth medium containing ^{13}C -, ^{15}N - and/or ^2H -labeled substrates. In certain instances, bacterial growth media consists of ^{13}C -labeled glucose and/or ^{15}N -labeled ammonium salts dissolved in D_2O where necessary. Kay, L. et al., *Science*, 249:411 (1990)
15 and references therein and Bax, A., *J. Am. Chem. Soc.*, 115, 4369 (1993). More recently, isotopically labeled media especially adapted for the labeling of bacterially produced macromolecules have been described. See U.S. Pat. No. 5,324,658.

The goal of these methods has been to achieve universal and/or random isotopic enrichment of all of the amino acids of the protein. By contrast, other methods allow only
20 certain residues to be relatively enriched in ^1H , ^2H , ^{13}C and ^{15}N . For example, Kay et al., *J. Mol. Biol.*, 263, 627-636 (1996) and Kay et al., *J. Am. Chem. Soc.*, 119, 7599-7600 (1997) have described methods whereby isoleucine, alanine, valine and leucine residues in a protein may be labeled with ^2H , ^{13}C and ^{15}N , and may be specifically labeled with ^1H at the terminal methyl position. In this way, study of the proton-proton interactions between
25 some amino acids may be facilitated. Similarly, a cell-free system has been described by Yokoyama et al., *J. Biomol. NMR*, 6(2), 129-134 (1995), wherein a transcription-translation system derived from *E. coli* was used to express human Ha-Ras protein incorporating ^{15}N into serine and/or aspartic acid.

Techniques for producing isotopically labeled proteins and macromolecules, such as
30 glycoproteins, in mammalian or insect cells have been described. See U.S. Pat. Nos. 5,393,669 and 5,627,044; Weller, C. T., *Biochem.*, 35, 8815-23 (1996) and Lustbader, J. W., *J. Biomol. NMR*, 7, 295-304 (1996). Other methods for producing polypeptides and other molecules with labels appropriate for NMR are known in the art.

The present invention contemplates using a variety of solvents which are appropriate for NMR. For ^1H NMR, a deuterium lock solvent may be used. Exemplary deuterium lock solvents include acetone (CD_3COCD_3), chloroform (CDCl_3), dichloro methane (CD_2Cl_2), methylnitrile (CD_3CN), benzene (C_6D_6), water (D_2O), diethylether ((CD_3CD_2) $_2\text{O}$), dimethylether ((CD_3) $_2\text{O}$), N,N-dimethylformamide ((CD_3) $_2\text{NCDO}$), dimethyl sulfoxide (CD_3SOCD_3), ethanol ($\text{CD}_3\text{CD}_2\text{OD}$), methanol (CD_3OD), tetrahydrofuran ($\text{C}_4\text{D}_8\text{O}$), toluene ($\text{C}_6\text{D}_5\text{CD}_3$), pyridine ($\text{C}_5\text{D}_5\text{N}$) and cyclohexane (C_6H_{12}). For example, the present invention contemplates a composition comprising a polypeptide of the invention and a deuterium lock solvent.

10 The 2-dimensional ^1H - ^{15}N HSQC (Heteronuclear Single Quantum Correlation) spectrum provides a diagnostic fingerprint of conformational state, aggregation level, state of protein folding, and dynamic properties of a polypeptide (Yee et al, PNAS 99, 1825-30 (2002)). Polypeptides in aqueous solution usually populate an ensemble of 3-dimensional structures which can be determined by NMR. When the polypeptide is a stable globular
15 protein or domain of a protein, then the ensemble of solution structures is one of very closely related conformations. In this case, one peak is expected for each non-proline residue with a dispersion of resonance frequencies with roughly equal intensity. Additional pairs of peaks from side-chain NH_2 groups are also often observed, and correspond to the approximate number of Gln and Asn residues in the protein. This type of HSQC spectra
20 usually indicates that the protein is amenable to structure determination by NMR methods.

If the HSQC spectrum shows well-dispersed peaks but there are either too few or too many in number, and/or the peak intensities differ throughout the spectrum, then the protein likely does not exist in a single globular conformation. Such spectral features are indicative of conformational heterogeneity with slow or nonexistent inter-conversion
25 between states (too many peaks) or the presence of dynamic processes on an intermediate timescale that can broaden and obscure the NMR signals. Proteins with this type of spectrum can sometimes be stabilized into a single conformation by changing either the protein construct, the solution conditions, temperature or by binding of another molecule.

The ^1H - ^{15}N HSQC can also indicate whether a protein has formed large nonspecific
30 aggregates or has dynamic properties. Alternatively, proteins that are largely unfolded, e.g., having very little regular secondary structure, result in ^1H - ^{15}N HSQC spectra in which the peaks are all very narrow and intense, but have very little spectral dispersion in the ^{15}N -dimension. This reflects the fact that many or most of the amide groups of amino acids in

unfolded polypeptides are solvent exposed and experience similar chemical environments resulting in similar ^1H chemical shifts.

The use of the ^1H - ^{15}N HSQC, can thus allow the rapid characterization of the conformational state, aggregation level, state of protein folding, and dynamic properties of a polypeptide. Additionally, other 2D spectra such as ^1H - ^{13}C HSQC, or HNCQ spectra can also be used in a similar manner. Further use of the ^1H - ^{15}N HSQC combined with relaxation measurements can reveal the molecular rotational correlation time and dynamic properties of polypeptides. The rotational correlation time is proportional to size of the protein and therefore can reveal if it forms specific homo-oligomers such as homodimers, homotetramers, etc.

The structure of stable globular proteins can be determined through a series of well-described procedures. For a general review of structure determination of globular proteins in solution by NMR spectroscopy, see Wüthrich, *Science* 243: 45-50 (1989). See also, Billeter et al., *J. Mol. Biol.* 155: 321-346 (1982). Current methods for structure determination usually require the complete or nearly complete sequence-specific assignment of ^1H -resonance frequencies of the protein and subsequent identification of approximate inter-hydrogen distances (from nuclear Overhauser effect (NOE) spectra) for use in restrained molecular dynamics calculations of the protein conformation. One approach for the analysis of NMR resonance assignments was first outlined by Wüthrich, Wagner and co-workers (Wüthrich, "NMR of proteins and nucleic acids" Wiley, New York, New York (1986); Wüthrich, *Science* 243: 45-50 (1989); Billeter et al., *J. Mol. Biol.* 155: 321-346 (1982)). Newer methods for determining the structures of globular proteins include the use of residual dipolar coupling restraints (Tian et al., *J Am Chem Soc.* 2001 Nov 28;123(47):11791-6; Bax et al, *Methods Enzymol.* 2001;339:127-74) and empirically derived conformational restraints (Zweckstetter & Bax, *J Am Chem Soc.* 2001 Sep 26;123(38):9490-1). It has also been shown that it may be possible to determine structures of globular proteins using only un-assigned NOE measurements. NMR may also be used to determine ensembles of many inter-converting, unfolded conformations (Choy and Forman-Kay, *J Mol Biol.* 2001 May 18;308(5):1011-32).

NMR analysis of a polypeptide in the presence and absence of a test compound (e.g., a polypeptide, nucleic acid or small molecule) may be used to characterize interactions between a polypeptide and another molecule. Because the ^1H - ^{15}N HSQC spectrum and other simple 2D NMR experiments can be obtained very quickly (on the

order of minutes depending on protein concentration and NMR instrumentation), they are very useful for rapidly testing whether a polypeptide is able to bind to another molecule. Changes in the resonance frequency (in one or both dimensions) of one or more peaks in the HSQC spectrum indicate an interaction with another molecule. Often only a subset of the peaks will have changes in resonance frequency upon binding to another molecule, allowing one to map onto the structure those residues directly involved in the interaction or involved in conformational changes as a result of the interaction. If the interacting molecule is relatively large (protein or nucleic acid) the peak widths will also broaden due to the increased rotational correlation time of the complex. In some cases the peaks involved in the interaction may actually disappear from the NMR spectrum if the interacting molecule is in intermediate exchange on the NMR timescale (i.e., exchanging on and off the polypeptide at a frequency that is similar to the resonance frequency of the monitored nuclei).

To facilitate the acquisition of NMR data on a large number of compounds (e.g., a library of synthetic or naturally-occurring small organic compounds), a sample changer may be employed. Using the sample changer, a larger number of samples, numbering 60 or more, may be run unattended. To facilitate processing of the NMR data, computer programs are used to transfer and automatically process the multiple one-dimensional NMR data.

In one embodiment, the invention provides a screening method for identifying small molecules capable of interacting with a polypeptide of the invention. In one example, the screening process begins with the generation or acquisition of either a T_2 -filtered or a diffusion-filtered one-dimensional proton spectrum of the compound or mixture of compounds. Means for generating T_2 -filtered or diffusion-filtered one-dimensional proton spectra are well known in the art (see, e.g., S. Meiboom and D. Gill, *Rev. Sci. Instrum.* 29:688(1958), S. J. Gibbs and C. S. Johnson, Jr. *J. Main. Reson.* 93:395-402 (1991) and A. S. Altieri, et al. *J. Am. Chem. Soc.* 117: 7566-7567 (1995)).

Following acquisition of the first spectrum for the molecules, the ^{15}N - or ^{13}C -labeled polypeptide is exposed to one or more molecules. Where more than one test compound is to be tested simultaneously, it is preferred to use a library of compounds such as a plurality of small molecules. Such molecules are typically dissolved in perdeuterated dimethylsulfoxide. The compounds in the library may be purchased from vendors or created according to desired needs.

Individual compounds may be selected inter alia on the basis of size and molecular diversity for maximizing the possibility of discovering compounds that interact with widely diverse binding sites of a polypeptide of the invention.

5 The NMR screening process of the present invention utilizes a range of test compound concentrations, e.g., from about 0.05 to about 1.0 mM. At those exemplary concentrations, compounds which are acidic or basic may significantly change the pH of buffered protein solutions. Chemical shifts are sensitive to pH changes as well as direct binding interactions, and false-positive chemical shift changes, which are not the result of test compound binding but of changes in pH, may therefore be observed. It may therefore
10 be necessary to ensure that the pH of the buffered solution does not change upon addition of the test compound.

Following exposure of the test compounds to a polypeptide (e.g., the target molecule for the experiment) a second one-dimensional T_2 - or diffusion-filtered spectrum is generated. For the T_2 -filtered approach, that second spectrum is generated in the same
15 manner as set forth above. The first and second spectra are then compared to determine whether there are any differences between the two spectra. Differences in the one-dimensional T_2 -filtered spectra indicate that the compound is binding to, or otherwise interacting with, the target molecule. Those differences are determined using standard procedures well known in the art. For the diffusion-filtered method, the second spectrum is
20 generated by looking at the spectral differences between low and high gradient strengths—thus selecting for those compounds whose diffusion rates are comparable to that observed in the absence of target molecule.

To discover additional molecules that bind to the protein, molecules are selected for testing based on the structure/activity relationships from the initial screen and/or structural
25 information on the initial leads when bound to the protein. By way of example, the initial screening may result in the identification of compounds, all of which contain an aromatic ring. The second round of screening would then use other aromatic molecules as the test compounds.

In another embodiment, the methods of the invention utilize a process for detecting
30 the binding of one ligand to a polypeptide in the presence of a second ligand. In accordance with this embodiment, a polypeptide is bound to the second ligand before exposing the polypeptide to the test compounds.

For more information on NMR methods encompassed by the present invention, see also: U.S. Patent Nos. 5,668,734; 6,194,179; 6,162,627; 6,043,024; 5,817,474; 5,891,642; 5,989,827; 5,891,643; 6,077,682; WO 00/05414; WO 99/22019; Cavanagh, et al., Protein NMR Spectroscopy, Principles and Practice, 1996, Academic Press; Clore, et al., NMR of
5 Proteins. In Topics in Molecular and Structural Biology, 1993, S. Neidle, Fuller, W., and Cohen, J.S., eds., Macmillan Press, Ltd., London; and Christendat et al., Nature Structural Biology 7: 903-909 (2000).

(c) Analysis of Proteins by X-ray Crystallography

(i) X-ray Structure Determination

10 Exemplary methods for obtaining the three dimensional structure of the crystalline form of a molecule or complex are described herein and, in view of this specification, variations on these methods will be apparent to those skilled in the art (see Ducruix and Geige 1992, IRL Press, Oxford, England).

A variety of methods involving x-ray crystallography are contemplated by the
15 present invention. For example, the present invention contemplates producing a crystallized polypeptide of the invention, or a fragment thereof, by: (a) introducing into a host cell an expression vector comprising a nucleic acid encoding for a polypeptide of the invention, or a fragment thereof; (b) culturing the host cell in a cell culture medium to express the polypeptide or fragment; (c) isolating the polypeptide or fragment from the cell
20 culture; and (d) crystallizing the polypeptide or fragment thereof. Alternatively, the present invention contemplates determining the three dimensional structure of a crystallized polypeptide of the invention, or a fragment thereof, by: (a) crystallizing a polypeptide of the invention, or a fragment thereof, such that the crystals will diffract x-rays to a resolution of 3.5 Å or better; and (b) analyzing the polypeptide or fragment by x-ray diffraction to
25 determine the three-dimensional structure of the crystallized polypeptide.

X-ray crystallography techniques generally require that the protein molecules be available in the form of a crystal. Crystals may be grown from a solution containing a purified polypeptide of the invention, or a fragment thereof (e.g., a stable domain), by a variety of conventional processes. These processes include, for example, batch, liquid,
30 bridge, dialysis, vapour diffusion (e.g., hanging drop or sitting drop methods). (See for example, McPherson, 1982 John Wiley, New York; McPherson, 1990, Eur. J. Biochem. 189: 1-23; Webber. 1991, Adv. Protein Chem. 41:1-36).

In certain embodiments, native crystals of the invention may be grown by adding precipitants to the concentrated solution of the polypeptide. The precipitants are added at a concentration just below that necessary to precipitate the protein. Water may be removed by controlled evaporation to produce precipitating conditions, which are maintained until
5 crystal growth ceases.

The formation of crystals is dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions or ligands to the protein. In addition, the sequence of the polypeptide being crystallized will have a significant affect on the success of obtaining
10 crystals. Many routine crystallization experiments may be needed to screen all these parameters for the few combinations that might give crystal suitable for x-ray diffraction analysis (See, for example, Jancarik, J & Kim, S.H., J. Appl. Cryst. 1991 24: 409-411).

Crystallization robots may automate and speed up the work of reproducibly setting up large number of crystallization experiments. Once some suitable set of conditions for
15 growing the crystal are found, variations of the condition may be systematically screened in order to find the set of conditions which allows the growth of sufficiently large, single, well ordered crystals. In certain instances, a polypeptide of the invention is co-crystallized with a compound that stabilizes the polypeptide.

A number of methods are available to produce suitable radiation for x-ray
20 diffraction. For example, x-ray beams may be produced by synchrotron rings where electrons (or positrons) are accelerated through an electromagnetic field while traveling at close to the speed of light. Because the admitted wavelength may also be controlled, synchrotrons may be used as a tunable x-ray source (Hendrickson WA., Trends Biochem Sci 2000 Dec; 25(12):637-43). For less conventional Laue diffraction studies,
25 polychromatic x-rays covering a broad wavelength window are used to observe many diffraction intensities simultaneously (Stoddard, B. L., Curr. Opin. Struct Biol 1998 Oct; 8(5):612-8). Neutrons may also be used for solving protein crystal structures (Gutberlet T, Heinemann U & Steiner M., Acta Crystallogr D 2001;57: 349-54).

Before data collection commences, a protein crystal may be frozen to protect it from
30 radiation damage. A number of different cryo-protectants may be used to assist in freezing the crystal, such as methyl pentanediol (MPD), isopropanol, ethylene glycol, glycerol, formate, citrate, mineral oil, or a low-molecular-weight polyethylene glycol (PEG). The present invention contemplates a composition comprising a polypeptide of the invention

and a cryo-protectant. As an alternative to freezing the crystal, the crystal may also be used for diffraction experiments performed at temperatures above the freezing point of the solution. In these instances, the crystal may be protected from drying out by placing it in a narrow capillary of a suitable material (generally glass or quartz) with some of the crystal growth solution included in order to maintain vapour pressure.

5 X-ray diffraction results may be recorded by a number of ways known to one of skill in the art. Examples of area electronic detectors include charge coupled device detectors, multi-wire area detectors and phosphorimager detectors (Amemiya, Y, 1997. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 233-243; Westbrook, E. M.,
10 Naday, I. 1997. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 244-268; 1997. Kahn, R. & Fourme, R. Methods in Enzymology, Vol. 276. Academic Press, San Diego, pp. 268-286).

A suitable system for laboratory data collection might include a Bruker AXS Proteum R system, equipped with a copper rotating anode source, Confocal Max-Flux™
15 optics and a SMART 6000 charge coupled device detector. Collection of x-ray diffraction patterns are well documented by those skilled in the art (See, for example, Ducruix and Geige, 1992, IRL Press, Oxford, England).

The theory behind diffraction by a crystal upon exposure to x-rays is well known. Because phase information is not directly measured in the diffraction experiment, and is
20 needed to reconstruct the electron density map, methods that can recover this missing information are required. One method of solving structures *ab initio* are the real / reciprocal space cycling techniques. Suitable real / reciprocal space cycling search programs include shake-and-bake (Weeks CM, DeTitta GT, Hauptman HA, Thuman P, Miller R Acta Crystallogr A 1994; V50: 210-20).

25 Other methods for deriving phases may also be needed. These techniques generally rely on the idea that if two or more measurements of the same reflection are made where strong, measurable, differences are attributable to the characteristics of a small subset of the atoms alone, then the contributions of other atoms can be, to a first approximation, ignored, and positions of these atoms may be determined from the difference in scattering by one of
30 the above techniques. Knowing the position and scattering characteristics of those atoms, one may calculate what phase the overall scattering must have had to produce the observed differences.

One version of this technique is isomorphous replacement technique, which requires the introduction of new, well ordered, x-ray scatterers into the crystal. These additions are usually heavy metal atoms, (so that they make a significant difference in the diffraction pattern); and if the additions do not change the structure of the molecule or of the crystal cell, the resulting crystals should be isomorphous. Isomorphous replacement experiments are usually performed by diffusing different heavy-metal metals into the channels of a pre-existing protein crystal. Growing the crystal from protein that has been soaked in the heavy atom is also possible (Petsko, G.A., 1985. *Methods in Enzymology*, Vol. 114. Academic Press, Orlando, pp. 147-156). Alternatively, the heavy atom may also be reactive and attached covalently to exposed amino acid side chains (such as the sulfur atom of cysteine) or it may be associated through non-covalent interactions. It is sometimes possible to replace endogenous light metals in metallo-proteins with heavier ones, e.g., zinc by mercury, or calcium by samarium (Petsko, G.A., 1985. *Methods in Enzymology*, Vol. 114. Academic Press, Orlando, pp. 147-156). Exemplary sources for such heavy compounds include, without limitation, sodium bromide, sodium selenate, trimethyl lead acetate, mercuric chloride, methyl mercury acetate, platinum tetracyanide, platinum tetrachloride, nickel chloride, and europium chloride.

A second technique for generating differences in scattering involves the phenomenon of anomalous scattering. X-rays that cause the displacement of an electron in an inner shell to a higher shell are subsequently rescattered, but there is a time lag that shows up as a phase delay. This phase delay is observed as a (generally quite small) difference in intensity between reflections known as Friedel mates that would be identical if no anomalous scattering were present. A second effect related to this phenomenon is that differences in the intensity of scattering of a given atom will vary in a wavelength dependent manner, given rise to what are known as dispersive differences. In principle anomalous scattering occurs with all atoms, but the effect is strongest in heavy atoms, and may be maximized by using x-rays at a wavelength where the energy is equal to the difference in energy between shells. The technique therefore requires the incorporation of some heavy atom much as is needed for isomorphous replacement, although for anomalous scattering a wider variety of atoms are suitable, including lighter metal atoms (copper, zinc, iron) in metallo-proteins. One method for preparing a protein for anomalous scattering involves replacing the methionine residues in whole or in part with selenium containing seleno-methionine. Soaks with halide salts such as bromides and other non-reactive ions

may also be effective (Dauter Z, Li M, Wlodawer A., *Acta Crystallogr D* 2001; 57: 239-49).

In another process, known as multiple anomalous scattering or MAD, two to four suitable wavelengths of data are collected. (Hendrickson, W.A. and Ogata, C.M. 1997
5 *Methods in Enzymology* 276, 494 – 523). Phasing by various combinations of single and multiple isomorphous and anomalous scattering are possible too. For example, SIRAS (single isomorphous replacement with anomalous scattering) utilizes both the isomorphous and anomalous differences for one derivative to derive phases. More traditionally, several different heavy atoms are soaked into different crystals to get sufficient phase information
10 from isomorphous differences while ignoring anomalous scattering, in the technique known as multiple isomorphous replacement (MIR) (Petsko, G.A., 1985. *Methods in Enzymology*, Vol. 114. Academic Press, Orlando, pp. 147-156).

Additional restraints on the phases may be derived from density modification techniques. These techniques use either generally known features of electron density
15 distribution or known facts about that particular crystal to improve the phases. For example, because protein regions of the crystal scatter more strongly than solvent regions, solvent flattening/flipping may be used to adjust phases to make solvent density a uniform flat value (Zhang, K. Y. J., Cowtan, K. and Main, P. *Methods in Enzymology* 277, 1997 Academic Press, Orlando pp 53-64). If more than one molecule of the protein is present in
20 the asymmetric unit, the fact that the different molecules should be virtually identical may be exploited to further reduce phase error using non-crystallographic symmetry averaging (Villieux, F. M. D. and Read, R. J. *Methods in Enzymology* 277, 1997 Academic Press, Orlando pp18-52). Suitable programs for performing these processes include DM and other programs of the CCP4 suite (Collaborative Computational Project, Number 4. 1994. *Acta*
25 *Cryst. D*50, 760-763) and CNX.

The unit cell dimensions, symmetry, vector amplitude and derived phase information can be used in a Fourier transform function to calculate the electron density in the unit cell, i.e., to generate an experimental electron density map. This may be accomplished using programs of the CNX or CCP4 packages. The resolution is measured
30 in Ångstrom (Å) units, and is closely related to how far apart two objects need to be before they can be reliably distinguished. The smaller this number is, the higher the resolution and therefore the greater the amount of detail that can be seen. Preferably, crystals of the

invention diffract x-rays to a resolution of better than about 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5 Å or better.

As used herein, the term "modeling" includes the quantitative and qualitative analysis of molecular structure and/or function based on atomic structural information and interaction models. The term "modeling" includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models.

Model building may be accomplished by either the crystallographer using a computer graphics program such as TURBO or O (Jones, T.A. et al., *Acta Crystallogr. A* 47, 100-119, 1991) or, under suitable circumstances, by using a fully automated model building program, such as wARP (Anastassis Perrakis, Richard Morris & Victor S. Lamzin; *Nature Structural Biology*, May 1999 Volume 6 Number 5 pp 458 – 463) or MAID (Levitt, D. G., *Acta Crystallogr. D* 2001 V57: 1013-9). This structure may be used to calculate model-derived diffraction amplitudes and phases. The model-derived and experimental diffraction amplitudes may be compared and the agreement between them can be described by a parameter referred to as R-factor. A high degree of correlation in the amplitudes corresponds to a low R-factor value, with 0.0 representing exact agreement and 0.59 representing a completely random structure. Because the R-factor may be lowered by introducing more free parameters into the model, an unbiased, cross-correlated version of the R-factor known as the R-free gives a more objective measure of model quality. For the calculation of this parameter a subset of reflections (generally around 10%) are set aside at the beginning of the refinement and not used as part of the refinement target. These reflections are then compared to those predicted by the model (Kleywegt GJ, Brunger AT, *Structure* 1996 Aug 15;4(8):897-904).

The model may be improved using computer programs that maximize the probability that the observed data was produced from the predicted model, while simultaneously optimizing the model geometry. For example, the CNX program may be used for model refinement, as can the XPLOR program (1992, *Nature* 355:472-475, G.N. Murshudov, A.A. Vagin and E.J. Dodson, (1997) *Acta Cryst. D* 53, 240-255). In order to maximize the convergence radius of refinement, simulated annealing refinement using torsion angle dynamics may be employed in order to reduce the degrees of freedom of motion of the model (Adams PD, Pannu NS, Read RJ, Brunger AT., *Proc Natl Acad Sci U*

S A 1997 May 13;94(10):5018-23). Where experimental phase information is available (e.g. where MAD data was collected) Hendrickson-Lattman phase probability targets may be employed. Isotropic or anisotropic domain, group or individual temperature factor refinement, may be used to model variance of the atomic position from its mean. Well defined peaks of electron density not attributable to protein atoms are generally modeled as water molecules. Water molecules may be found by manual inspection of electron density maps, or with automatic water picking routines. Additional small molecules, including ions, cofactors, buffer molecules or substrates may be included in the model if sufficiently unambiguous electron density is observed in a map.

10 In general, the R-free is rarely as low as 0.15 and may be as high as 0.35 or greater for a reasonably well-determined protein structure. The residual difference is a consequence of approximations in the model (inadequate modeling of residual structure in the solvent, modeling atoms as isotropic Gaussian spheres, assuming all molecules are identical rather than having a set of discrete conformers, etc.) and errors in the data
15 (Lattman EE., *Proteins* 1996; 25: i-ii). In refined structures at high resolution, there are usually no major errors in the orientation of individual residues, and the estimated errors in atomic positions are usually around 0.1 - 0.2 up to 0.3 Å.

The three dimensional structure of a new crystal may be modeled using molecular replacement. The term "molecular replacement" refers to a method that involves generating
20 a preliminary model of a molecule or complex whose structure coordinates are unknown, by orienting and positioning a molecule whose structure coordinates are known within the unit cell of the unknown crystal, so as best to account for the observed diffraction pattern of the unknown crystal. Phases may then be calculated from this model and combined with the observed amplitudes to give an approximate Fourier synthesis of the structure whose
25 coordinates are unknown. This, in turn, can be subject to any of the several forms of refinement to provide a final, accurate structure of the unknown crystal. Lattman, E., "Use of the Rotation and Translation Functions", in *Methods in Enzymology*, 115, pp. 55-77 (1985); M. G. Rossmann, ed., "The Molecular Replacement Method", *Int. Sci. Rev. Ser.*, No. 13, Gordon & Breach, New York, (1972).

30 Commonly used computer software packages for molecular replacement are CNX, X-PLOR (Brunger 1992, *Nature* 355: 472-475), AMoRE (Navaza, 1994, *Acta Crystallogr. A* 50:157-163), the CCP4 package, the MERLOT package (P.M.D. Fitzgerald, *J. Appl. Cryst.*, Vol. 21, pp. 273-278, 1988) and XTALVIEW (McCree et al (1992) *J. Mol. Graphics*

10: 44-46). The quality of the model may be analyzed using a program such as PROCHECK or 3D-Profiler (Laskowski et al 1993 J. Appl. Cryst. 26:283-291; Luthy R. et al, Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991).

Homology modeling (also known as comparative modeling or knowledge-based
5 modeling) methods may also be used to develop a three dimensional model from a polypeptide sequence based on the structures of known proteins. The method utilizes a computer model of a known protein, a computer representation of the amino acid sequence of the polypeptide with an unknown structure, and standard computer representations of the structures of amino acids. This method is well known to those skilled in the art (Greer,
10 1985, Science 228, 1055; Bundell et al 1988, Eur. J. Biochem. 172, 513; Knighton et al., 1992, Science 258:130-135, <http://biochem.vt.edu/courses/~modeling/homology.htm>). Computer programs that can be used in homology modeling are QUANTA and the Homology module in the Insight II modeling package distributed by Molecular Simulations Inc, or MODELLER (Rockefeller University, [www.iucr.ac.uk/sinris-top/logical/prg-](http://www.iucr.ac.uk/sinris-top/logical/prg-modeller.html)
15 [modeller.html](http://www.iucr.ac.uk/sinris-top/logical/prg-modeller.html)).

Once a homology model has been generated it is analyzed to determine its correctness. A computer program available to assist in this analysis is the Protein Health module in QUANTA which provides a variety of tests. Other programs that provide structure analysis along with output include PROCHECK and 3D-Profiler (Luthy R. et al,
20 Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991). Once any irregularities have been resolved, the entire structure may be further refined.

Other molecular modeling techniques may also be employed in accordance with this invention. See, e.g., Cohen, N. C. *et al*, J. Med. Chem., 33, pp. 883-894 (1990). See also, Navix, M. A. and M. A. Marko, Current Opinions in Structural Biology, 2, pp. 202-210
25 (1992).

Under suitable circumstances, the entire process of solving a crystal structure may be accomplished in an automated fashion by a system such as ELVES (<http://ucxray.berkeley.edu/~jamesh/elves/index.html>) with little or no user intervention.

(ii) X-ray Structure

30 The present invention provides methods for determining some or all of the structural coordinates for amino acids of a polypeptide of the invention, or a complex thereof.

In another aspect, the present invention provides methods for identifying a druggable region of a polypeptide of the invention. For example, one such method

includes: (a) obtaining crystals of a polypeptide of the invention or a fragment thereof such that the three dimensional structure of the crystallized protein can be determined to a resolution of 3.5 Å or better; (b) determining the three dimensional structure of the crystallized polypeptide or fragment using x-ray diffraction; and (c) identifying a druggable
5 region of a polypeptide of the invention based on the three-dimensional structure of the polypeptide or fragment.

A three dimensional structure of a molecule or complex may be described by the set of atoms that best predict the observed diffraction data (that is, which possesses a minimal R value). Files may be created for the structure that defines each atom by its chemical
10 identity, spatial coordinates in three dimensions, root mean squared deviation from the mean observed position and fractional occupancy of the observed position.

Those of skill in the art understand that a set of structure coordinates for an protein, complex or a portion thereof, is a relative set of points that define a shape in three dimensions. Thus, it is possible that an entirely different set of coordinates could define a
15 similar or identical shape. Moreover, slight variations in the individual coordinates may have little affect on overall shape. Such variations in coordinates may be generated because of mathematical manipulations of the structure coordinates. For example, structure coordinates could be manipulated by crystallographic permutations of the structure coordinates, fractionalization of the structure coordinates, integer additions or subtractions
20 to sets of the structure coordinates, inversion of the structure coordinates or any combination of the above. Alternatively, modifications in the crystal structure due to mutations, additions, substitutions, and/or deletions of amino acids, or other changes in any of the components that make up the crystal, could also yield variations in structure coordinates. Such slight variations in the individual coordinates will have little affect on
25 overall shape. If such variations are within an acceptable standard error as compared to the original coordinates, the resulting three-dimensional shape is considered to be structurally equivalent. It should be noted that slight variations in individual structure coordinates of a polypeptide of the invention or a complex thereof would not be expected to significantly alter the nature of modulators that could associate with a druggable region thereof. Thus,
30 for example, a modulator that bound to the active site of a polypeptide of the invention would also be expected to bind to or interfere with another active site whose structure coordinates define a shape that falls within the acceptable error.

A crystal structure of the present invention may be used to make a structural or computer model of the polypeptide, complex or portion thereof. A model may represent the secondary, tertiary and/or quaternary structure of the polypeptide, complex or portion. The configurations of points in space derived from structure coordinates according to the invention can be visualized as, for example, a holographic image, a stereodiagram, a model or a computer-displayed image, and the invention thus includes such images, diagrams or models.

(iii) Structural Equivalents

Various computational analyses can be used to determine whether a molecule or the active site portion thereof is structurally equivalent with respect to its three-dimensional structure, to all or part of a structure of a polypeptide of the invention or a portion thereof.

For the purpose of this invention, any molecule or complex or portion thereof, that has a root mean square deviation of conserved residue backbone atoms (N, C α , C, O) of less than about 1.75 Å, when superimposed on the relevant backbone atoms described by the reference structure coordinates of a polypeptide of the invention, is considered "structurally equivalent" to the reference molecule. That is to say, the crystal structures of those portions of the two molecules are substantially identical, within acceptable error. Alternatively, the root mean square deviation may be less than about 1.50, 1.40, 1.25, 1.0, 0.75, 0.5 or 0.35 Å.

The term "root mean square deviation" is understood in the art and means the square root of the arithmetic mean of the squares of the deviations. It is a way to express the deviation or variation from a trend or object.

In another aspect, the present invention provides a scalable three-dimensional configuration of points, at least a portion of said points, and preferably all of said points, derived from structural coordinates of at least a portion of a polypeptide of the invention and having a root mean square deviation from the structure coordinates of the polypeptide of the invention of less than 1.50, 1.40, 1.25, 1.0, 0.75, 0.5 or 0.35 Å. In certain embodiments, the portion of a polypeptide of the invention is 25%, 33%, 50%, 66%, 75%, 85%, 90% or 95% or more of the amino acid residues contained in the polypeptide.

In another aspect, the present invention provides a molecule or complex including a druggable region of a polypeptide of the invention, the druggable region being defined by a set of points having a root mean square deviation of less than about 1.75 Å from the structural coordinates for points representing (a) the backbone atoms of the amino acids

contained in a druggable region of a polypeptide of the invention, (b) the side chain atoms (and optionally the C α atoms) of the amino acids contained in such druggable region, or (c) all the atoms of the amino acids contained in such druggable region. In certain embodiments, only a portion of the amino acids of a druggable region may be included in the set of points, such as 25%, 33%, 50%, 66%, 75%, 85%, 90% or 95% or more of the amino acid residues contained in the druggable region. In certain embodiments, the root mean square deviation may be less than 1.50, 1.40, 1.25, 1.0, 0.75, 0.5, or 0.35 Å. In still other embodiments, instead of a druggable region, a stable domain, fragment or structural motif is used in place of a druggable region.

10 *(iv) Machine Displays and Machine Readable Storage Media*

The invention provides a machine-readable storage medium including a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, displays a graphical three-dimensional representation of any of the molecules or complexes, or portions thereof, of this invention. In another embodiment, the graphical three-dimensional representation of such molecule, complex or portion thereof includes the root mean square deviation of certain atoms of such molecule by a specified amount, such as the backbone atoms by less than 0.8 Å. In another embodiment, a structural equivalent of such molecule, complex, or portion thereof, may be displayed. In another embodiment, the portion may include a druggable region of the polypeptide of the invention.

According to one embodiment, the invention provides a computer for determining at least a portion of the structure coordinates corresponding to x-ray diffraction data obtained from a molecule or complex, wherein said computer includes: (a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates of a polypeptide of the invention; (b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises x-ray diffraction data from said molecule or complex; (c) a working memory for storing instructions for processing said machine-readable data of (a) and (b); (d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and (e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or

complex. In certain embodiments, the structural coordinates displayed are structurally equivalent to the structural coordinates of a polypeptide of the invention.

In an alternative embodiment, the machine-readable data storage medium includes a data storage material encoded with a first set of machine readable data which includes the
5 Fourier transform of the structure coordinates of a polypeptide of the invention or a portion thereof, and which, when using a machine programmed with instructions for using said data, can be combined with a second set of machine readable data including the x-ray diffraction pattern of a molecule or complex to determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

10 For example, a system for reading a data storage medium may include a computer including a central processing unit ("CPU"), a working memory which may be, e.g., RAM (random access memory) or "core" memory, mass storage memory (such as one or more disk drives or CD-ROM drives), one or more display devices (e.g., cathode-ray tube ("CRT") displays, light emitting diode ("LED") displays, liquid crystal displays ("LCDs"),
15 electroluminescent displays, vacuum fluorescent displays, field emission displays ("FEDs"), plasma displays, projection panels, etc.), one or more user input devices (e.g., keyboards, microphones, mice, touch screens, etc.), one or more input lines, and one or more output lines, all of which are interconnected by a conventional bidirectional system bus. The system may be a stand-alone computer, or may be networked (e.g., through local
20 area networks, wide area networks, intranets, extranets, or the internet) to other systems (e.g., computers, hosts, servers, etc.). The system may also include additional computer controlled devices such as consumer electronics and appliances.

Input hardware may be coupled to the computer by input lines and may be implemented in a variety of ways. Machine-readable data of this invention may be inputted
25 via the use of a modem or modems connected by a telephone line or dedicated data line. Alternatively or additionally, the input hardware may include CD-ROM drives or disk drives. In conjunction with a display terminal, a keyboard may also be used as an input device.

Output hardware may be coupled to the computer by output lines and may similarly
30 be implemented by conventional devices. By way of example, the output hardware may include a display device for displaying a graphical representation of an active site of this invention using a program such as QUANTA as described herein. Output hardware might

also include a printer, so that hard copy output may be produced, or a disk drive, to store system output for later use.

In operation, a CPU coordinates the use of the various input and output devices, coordinates data accesses from mass storage devices, accesses to and from working
5 memory, and determines the sequence of data processing steps. A number of programs may be used to process the machine-readable data of this invention. Such programs are discussed in reference to the computational methods of drug discovery as described herein. References to components of the hardware system are included as appropriate throughout the following description of the data storage medium.

10 Machine-readable storage devices useful in the present invention include, but are not limited to, magnetic devices, electrical devices, optical devices, and combinations thereof. Examples of such data storage devices include, but are not limited to, hard disk devices, CD devices, digital video disk devices, floppy disk devices, removable hard disk devices, magneto-optic disk devices, magnetic tape devices, flash memory devices, bubble
15 memory devices, holographic storage devices, and any other mass storage peripheral device. It should be understood that these storage devices include necessary hardware (e.g., drives, controllers, power supplies, etc.) as well as any necessary media (e.g., disks, flash cards, etc.) to enable the storage of data.

In one embodiment, the present invention contemplates a computer readable storage
20 medium comprising structural data, wherein the data include the identity and three-dimensional coordinates of a polypeptide of the invention or portion thereof. In another aspect, the present invention contemplates a database comprising the identity and three-dimensional coordinates of a polypeptide of the invention or a portion thereof. Alternatively, the present invention contemplates a database comprising a portion or all of
25 the atomic coordinates of a polypeptide of the invention or portion thereof.

(v) Structurally Similar Molecules and Complexes

Structural coordinates for a polypeptide of the invention can be used to aid in obtaining structural information about another molecule or complex. This method of the invention allows determination of at least a portion of the three-dimensional structure of
30 molecules or molecular complexes which contain one or more structural features that are similar to structural features of a polypeptide of the invention. Similar structural features can include, for example, regions of amino acid identity, conserved active site or binding site motifs, and similarly arranged secondary structural elements (e.g., α helices and β

sheets). Many of the methods described above for determining the structure of a polypeptide of the invention may be used for this purpose as well.

For the present invention, a "structural homolog" is a polypeptide that contains one or more amino acid substitutions, deletions, additions, or rearrangements with respect to the amino acid sequence of SEQ ID NO: 4 or other polypeptide of the invention, but that, when folded into its native conformation, exhibits or is reasonably expected to exhibit at least a portion of the tertiary (three-dimensional) structure of the polypeptide encoded by SEQ ID NO: 4 or such other polypeptide of the invention. For example, structurally homologous molecules can contain deletions or additions of one or more contiguous or noncontiguous amino acids, such as a loop or a domain. Structurally homologous molecules also include modified polypeptide molecules that have been chemically or enzymatically derivatized at one or more constituent amino acids, including side chain modifications, backbone modifications, and N- and C-terminal modifications including acetylation, hydroxylation, methylation, amidation, and the attachment of carbohydrate or lipid moieties, cofactors, and the like.

By using molecular replacement, all or part of the structure coordinates of a polypeptide of the invention can be used to determine the structure of a crystallized molecule or complex whose structure is unknown more quickly and efficiently than attempting to determine such information *ab initio*. For example, in one embodiment this invention provides a method of utilizing molecular replacement to obtain structural information about a molecule or complex whose structure is unknown including: (a) crystallizing the molecule or complex of unknown structure; (b) generating an x-ray diffraction pattern from said crystallized molecule or complex; and (c) applying at least a portion of the structure coordinates for a polypeptide of the invention to the x-ray diffraction pattern to generate a three-dimensional electron density map of the molecule or complex whose structure is unknown.

In another aspect, the present invention provides a method for generating a preliminary model of a molecule or complex whose structure coordinates are unknown, by orienting and positioning the relevant portion of a polypeptide of the invention within the unit cell of the crystal of the unknown molecule or complex so as best to account for the observed x-ray diffraction pattern of the crystal of the molecule or complex whose structure is unknown.

Structural information about a portion of any crystallized molecule or complex that is sufficiently structurally similar to a portion of a polypeptide of the invention may be resolved by this method. In addition to a molecule that shares one or more structural features with a polypeptide of the invention, a molecule that has similar bioactivity, such as the same catalytic activity, substrate specificity or ligand binding activity as a polypeptide of the invention, may also be sufficiently structurally similar to a polypeptide of the invention to permit use of the structure coordinates for a polypeptide of the invention to solve its crystal structure.

In another aspect, the method of molecular replacement is utilized to obtain structural information about a complex containing a polypeptide of the invention, such as a complex between a modulator and a polypeptide of the invention (or a domain, fragment, ortholog, homolog etc. thereof). In certain instances, the complex includes a polypeptide of the invention (or a domain, fragment, ortholog, homolog etc. thereof) co-complexed with a modulator. For example, in one embodiment, the present invention contemplates a method for making a crystallized complex comprising a polypeptide of the invention, or a fragment thereof, and a compound having a molecular weight of less than 5 kDa, the method comprising: (a) crystallizing a polypeptide of the invention such that the crystals will diffract x-rays to a resolution of 3.5 Å or better; and (b) soaking the crystal in a solution comprising the compound having a molecular weight of less than 5 kDa, thereby producing a crystallized complex comprising the polypeptide and the compound.

Using homology modeling, a computer model of a structural homolog or other polypeptide can be built or refined without crystallizing the molecule. For example, in another aspect, the present invention provides a computer-assisted method for homology modeling a structural homolog of a polypeptide of the invention including: aligning the amino acid sequence of a known or suspected structural homolog with the amino acid sequence of a polypeptide of the invention and incorporating the sequence of the homolog into a model of a polypeptide of the invention derived from atomic structure coordinates to yield a preliminary model of the homolog; subjecting the preliminary model to energy minimization to yield an energy minimized model; remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the homolog.

In another embodiment, the present invention contemplates a method for determining the crystal structure of a homolog of a polypeptide having SEQ ID NO: 2 or

SEQ ID NO: 4, or equivalent thereof, the method comprising: (a) providing the three dimensional structure of a crystallized polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof; (b) obtaining crystals of a homologous polypeptide comprising an amino acid sequence that is at least 80% identical to the amino acid sequence set forth in
5 SEQ ID NO: 2 or SEQ ID NO: 4 such that the three dimensional structure of the crystallized homologous polypeptide may be determined to a resolution of 3.5 Å or better; and (c) determining the three dimensional structure of the crystallized homologous polypeptide by x-ray crystallography based on the atomic coordinates of the three dimensional structure provided in step (a). In certain instances of the foregoing method, the
10 atomic coordinates for the homologous polypeptide have a root mean square deviation from the backbone atoms of the polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof, of not more than 1.5 Å for all backbone atoms shared in common with the homologous polypeptide and the polypeptide having SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof.

15 (vi) *NMR Analysis Using X-ray Structural Data*

In another aspect, the structural coordinates of a known crystal structure may be applied to nuclear magnetic resonance data to determine the three dimensional structures of polypeptides with uncharacterized or incompletely characterized structure. (See for example, Wuthrich, 1986, John Wiley and Sons, New York: 176-199; Pflugrath et al., 1986,
20 J. Molecular Biology 189: 383-386; Kline et al., 1986 J. Molecular Biology 189:377-382). While the secondary structure of a polypeptide may often be determined by NMR data, the spatial connections between individual pieces of secondary structure are not as readily determined. The structural coordinates of a polypeptide defined by x-ray crystallography can guide the NMR spectroscopist to an understanding of the spatial interactions between
25 secondary structural elements in a polypeptide of related structure. Information on spatial interactions between secondary structural elements can greatly simplify NOE data from two-dimensional NMR experiments. In addition, applying the structural coordinates after the determination of secondary structure by NMR techniques simplifies the assignment of NOE's relating to particular amino acids in the polypeptide sequence.

30 In an embodiment, the invention relates to a method of determining three dimensional structures of polypeptides with unknown structures, by applying the structural coordinates of a crystal of the present invention to nuclear magnetic resonance data of the unknown structure. This method comprises the steps of: (a) determining the secondary

structure of an unknown structure using NMR data; and (b) simplifying the assignment of through-space interactions of amino acids. The term "through-space interactions" defines the orientation of the secondary structural elements in the three dimensional structure and the distances between amino acids from different portions of the amino acid sequence. The term "assignment" defines a method of analyzing NMR data and identifying which amino acids give rise to signals in the NMR spectrum.

For all of this section on x-ray crystallography, see also Brooks et al. (1983) *J Comput Chem* 4:187-217; Weiner et al (1981) *J. Comput. Chem.* 106: 765; Eisenfield et al. (1991) *Am J Physiol* 261:C376-386; Lybrand (1991) *J Pharm Belg* 46:49-54; Froimowitz (1990) *Biotechniques* 8:640-644; Burbam et al. (1990) *Proteins* 7:99-111; Pedersen (1985) *Environ Health Perspect* 61:185-190; and Kini et al. (1991) *J Biomol Struct Dyn* 9:475-488; Ryckaert et al. (1977) *J Comput Phys* 23:327; Van Gunsteren et al. (1977) *Mol Phys* 34:1311; Anderson (1983) *J Comput Phys* 52:24; J. Mol. Biol. 48: 442-453, 1970; Dayhoff et al., *Meth. Enzymol.* 91: 524-545, 1983; Henikoff and Henikoff, *Proc. Nat. Acad. Sci. USA* 89: 10915-10919, 1992; J. Mol. Biol. 233: 716-738, 1993; *Methods in Enzymology*, Volume 276, *Macromolecular crystallography, Part A*, ISBN 0-12-182177-3 and Volume 277, *Macromolecular crystallography, Part B*, ISBN 0-12-182178-1, Eds. Charles W. Carter, Jr. and Robert M. Sweet (1997), Academic Press, San Diego; Pfuetzner, et al., *J. Biol. Chem.* 272: 430-434 (1997).

6. Interacting Proteins

The present invention also provides methods for isolating specific protein interactors of a polypeptide of the invention, and complexes comprising a polypeptide of the invention and one or more interacting proteins. In one aspect, the present invention contemplates an isolated protein complex comprising a polypeptide of the invention and at least one protein that interacts with the polypeptide of the invention. The protein may be naturally-occurring. The interacting protein may be of *E. faecalis* origin. Alternatively, the interacting protein may be of mammalian origin or human origin. Either the polypeptide of the invention or the interacting protein or both may be a fusion protein.

The present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of the invention or a fragment thereof, the method comprising: (a) exposing a sample to a solid substrate coupled to a polypeptide of the invention or a fragment thereof under conditions which promote protein-protein

interactions; (b) washing the solid substrate so as to remove any polypeptides interacting non-specifically with the polypeptide or fragment; (c) eluting the polypeptides which specifically interact with the polypeptide or fragment; and (d) identifying the interacting protein. The sample may be an extract of *E. faecalis*, a mammalian cell extract, a human
5 cell extract, a purified protein (or a fragment thereof), or a mixture of purified proteins (or fragments thereof). The interacting protein may be identified by a number of methods, including mass spectrometry or protein sequencing.

In another aspect, the present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of present invention or a fragment thereof,
10 the method comprising: (a) subjecting a sample to protein-affinity chromatography on multiple columns, the columns having a polypeptide of the invention or a fragment thereof coupled to the column matrix in varying concentrations, and eluting bound components of the extract from the columns; (b) separating the components to isolate a polypeptide capable of interacting with the polypeptide or fragment; and (c) analyzing the interacting
15 protein by mass spectrometry to identify the interacting protein. In certain instances, the foregoing method will use polyacrylamide gel electrophoresis without SDS.

In another aspect, the present invention contemplates a method for identifying a protein capable of interacting with a polypeptide of the invention, the method comprising:
(a) subjecting a cellular extract or extracellular fluid to protein-affinity chromatography on
20 multiple columns, the columns having a polypeptide of the invention or a fragment thereof coupled to the column matrix in varying concentrations, and eluting bound components of the extract from the columns; (b) gel-separating the components to isolate an interacting protein; wherein the interacting protein is observed to vary in amount in direct relation to the concentration of coupled polypeptide or fragment; (c) digesting the interacting protein
25 to give corresponding peptides; (d) analyzing the peptides by MALDI-TOF mass spectrometry or post source decay to determine the peptide masses; and (d) performing correlative database searches with the peptide, or peptide fragment, masses, whereby the interacting protein is identified based on the masses of the peptides or peptide fragments. The foregoing method may include the further step of including the identifies of any
30 interacting proteins into a relational database.

In another aspect, the invention further contemplates a method for identifying modulators of a protein complex, the method comprising: (a) contacting a protein complex comprising a polypeptide of the invention and an interacting protein with one or more test

compounds; and (b) determining the effect of the test compound on (i) the activity of the protein complex, (ii) the amount of the protein complex, (iii) the stability of the protein complex, (iv) the conformation of the protein complex, (v) the activity of at least one polypeptide included in the protein complex, (vi) the conformation of at least one polypeptide included in the protein complex, (vii) the intracellular localization of the protein complex or a component thereof, (viii) the transcription level of a gene dependent on the complex, and/or (ix) the level of second messenger levels in a cell; thereby identifying modulators of the protein complex. The foregoing method may be carried out *in vitro* or *in vivo* as appropriate.

Typically, it will be desirable to immobilize a polypeptide of the invention to facilitate separation of complexes comprising a polypeptide of the invention from uncomplexed forms of the interacting proteins, as well as to accommodate automation of the assay. The polypeptide of the invention, or ligand, may be immobilized onto a solid support (e.g., column matrix, microtiter plate, slide, etc.). In certain embodiments, the ligand may be purified. In certain instances, a fusion protein may be provided which adds a domain that permits the ligand to be bound to a support.

In various *in vitro* embodiments, the set of proteins engaged in a protein-protein interaction comprises a cell extract, a clarified cell extract, or a reconstituted protein mixture of at least semi-purified proteins. By semi-purified, it is meant that the proteins utilized in the reconstituted mixture have been previously separated from other cellular or viral proteins. For instance, in contrast to cell lysates, the proteins involved in a protein-protein interaction are present in the mixture to at least about 50% purity relative to all other proteins in the mixture, and more preferably are present in greater, even 90-95%, purity. In certain embodiments of the subject method, the reconstituted protein mixture is derived by mixing highly purified proteins such that the reconstituted mixture substantially lacks other proteins (such as of cellular or viral origin) which might interfere with or otherwise alter the ability to measure activity resulting from the given protein-protein interaction.

Complex formation involving a polypeptide of the invention and another component polypeptide or a substrate polypeptide, may be detected by a variety of techniques. For instance, modulation in the formation of complexes can be quantitated using, for example, detectably labeled proteins (e.g. radiolabeled, fluorescently labeled, or enzymatically labeled), by immunoassay, or by chromatographic detection.

The present invention also provides assays for identifying molecules which are modulators of a protein-protein interaction involving a polypeptide of the invention, or are a modulator of the role of the complex comprising a polypeptide of the invention in the infectivity or pathogenicity of *E. faecalis*. In one embodiment, the assay detects agents
5 which inhibit formation or stabilization of a protein complex comprising a polypeptide of the invention and one or more additional proteins. In another embodiment, the assay detects agents which modulate the intrinsic biological activity of a protein complex comprising a polypeptide of the invention, such as an enzymatic activity, binding to other cellular components, cellular compartmentalization, signal transduction, and the like. Such
10 modulators may be used, for example, in the treatment of *E. faecalis* related diseases or disorders. In certain embodiments, the compound is a mechanism based inhibitor which chemically alters one member of a protein-protein interaction involving a polypeptide of the invention and which is a specific inhibitor of that member, e.g. has an inhibition constant about 10-fold, 100-fold, or 1000-fold different compared to homologous proteins.

15 In one embodiment, proteins that interact with a polypeptide of the invention may be isolated using immunoprecipitation. A polypeptide of the invention may be expressed in *E. faecalis*, or in a heterologous system. The cells expressing a polypeptide of the invention are then lysed under conditions which maintain protein-protein interactions, and complexes comprising a polypeptide of the invention are isolated. For example, a polypeptide of the
20 invention may be expressed in mammalian cells, including human cells, in order to identify mammalian proteins that interact with a polypeptide of the invention and therefore may play a role in *E. faecalis* infectivity or proliferation. In one embodiment, a polypeptide of the invention is expressed in the cell type for which it is desirable to find interacting proteins. For example, a polypeptide of the invention may be expressed in *E. faecalis* in
25 order to find *E. faecalis* derived interacting proteins.

In an alternative embodiment, a polypeptide of the invention is expressed and purified and then mixed with a potential interacting protein or mixture of proteins to identify complex formation. The potential interacting protein may be a single purified or semi-purified protein, or a mixture of proteins, including a mixture of purified or semi-
30 purified proteins, a cell lysate, a clarified cell lysate, a semi-purified cell lysate, etc.

In certain embodiments, it may be desirable to use a tagged version of a polypeptide of the invention in order to facilitate isolation of complexes from the reaction mixture. Suitable tags for immunoprecipitation experiments include HA, myc, FLAG, HIS, GST,

protein A, protein G, etc. Immunoprecipitation from a cell lysate or other protein mixture may be carried out using an antibody specific for a polypeptide of the invention or using an antibody which recognizes a tag to which a polypeptide of the invention is fused (e.g., anti-HA, anti-myc, anti-FLAG, etc.). Antibodies specific for a variety of tags are known to the skilled artisan and are commercially available from a number of sources. In the case where a polypeptide of the invention is fused to a His, GST, or protein A/G tag, immunoprecipitation may be carried out using the appropriate affinity resin (e.g., beads functionalized with Ni, glutathione, Fc region of IgG, etc.). Test compounds which modulate a protein-protein interaction involving a polypeptide of the invention may be identified by carrying out the immunoprecipitation reaction in the presence and absence of the test agent and comparing the level and/or activity of the protein complex between the two reactions.

In another embodiment, proteins that interact with a polypeptide of the invention may be identified using affinity chromatography. Some examples of such chromatography are described in USSN 09/727,812, filed November 30, 2000, and the PCT Application filed November 30, 2001 and entitled "Methods for Systematic Identification of Protein-Protein Interactions and other Properties", which claims priority to such U.S. application.

In one aspect, for affinity chromatography using a solid support, a polypeptide of the invention or a fragment thereof may be attached by a variety of means known to those of skill in the art. For example, the polypeptide may be coupled directly (through a covalent linkage) to commercially available pre-activated resins as described in Formosa et al., *Methods in Enzymology* 1991, 208, 24-45; Sopta et al, *J. Biol. Chem.* 1985, 260, 10353-60; Archambault et al., *Proc. Natl. Acad. Sci. USA* 1997, 94, 14300-5. Alternatively, the polypeptide may be tethered to the solid support through high affinity binding interactions. If the polypeptide is expressed fused to a tag, such as GST, the fusion tag can be used to anchor the polypeptide to the matrix support, for example Sepharose beads containing immobilized glutathione. Solid supports that take advantage of these tags are commercially available.

In another aspect, the support to which a polypeptide may be immobilized is a soluble support, which may facilitate certain steps performed in the methods of the present invention. For example, the soluble support may be soluble in the conditions employed to create a binding interaction between a target and the polypeptide, and then used under

conditions in which it is a solid for elution of the proteins or other biological materials that bind to a polypeptide.

The concentration of the coupled polypeptide may have an affect on the sensitivity of the method. In certain embodiments, to detect interactions most efficiently, the concentration of the polypeptide bound to the matrix should be at least 10-fold higher than the K_d of the interaction. Thus, the concentration of the polypeptide bound to the matrix should be highest for the detection of the weakest protein-protein interactions. However, if the concentration of the immobilized polypeptide is not as high as may be ideal, it may still be possible to observe protein-protein interactions of interest by, for example, increasing the concentration of the polypeptide or other moiety that interacts with the coupled polypeptide. The level of detection will of course vary with each different polypeptide, interactor, conditions of the assay, etc. In certain instances, the interacting protein binds to the polypeptide with a K_d of about 10^{-5} M to about 10^{-8} M or 10^{-10} M.

In another aspect, the coupling may be done at various ratios of the polypeptide to the resin. An upper limit of the protein : resin ratio may be determined by the isoelectric point and the ionic nature of the protein, although it may be possible to achieve higher polypeptide concentrations by use of various methods.

In certain embodiments, several concentrations of the polypeptide immobilized on a solid or soluble support may be used. One advantage of using multiple concentrations, although not a requirement, is that one may be able to obtain an estimate for the strength of the protein-protein interaction that is observed in the affinity chromatography experiment. Another advantage of using multiple concentrations is that a binding curve which has the proper shape may indicate that the interaction that is observed is biologically important rather than a spurious interaction with denatured protein.

In one example of such an embodiment, a series of columns may be prepared with varying concentrations of polypeptide (mg polypeptide/ml resin volume). The number of columns employed may be between 2 to 8, 10, 12, 15, 25 or more, each with a different concentration of attached polypeptide. Larger numbers of columns may be used if appropriate for the polypeptide being examined, and multiple columns may be used with the same concentration as any methods may require. In certain embodiments, 4 to 6 columns are prepared with varying concentrations of polypeptide. In another aspect of this embodiment, two control columns may be prepared: one that contains no polypeptide and a second that contains the highest concentration of polypeptide but is not treated with extract.

After elution of the columns and separation of the eluent components (by one of the methods described below), it may be possible to distinguish the interacting proteins (if any) from the non-specific bound proteins as follows. The concentration of the interacting proteins, as determined by the intensity of the band on the gel, will increase proportionally to the increase in polypeptide concentration but will be missing from the second control column. This allows for the identification of unknown interacting proteins.

The method of the invention may be used for small-scale analysis. A variety of column sizes, types, and geometries may be used. In addition, other vessel shapes and sizes having a smaller scale than is usually found in laboratory experiments may be used as well, including a plurality of wells in a plate. For high throughput analysis, it is advantageous to use small volumes, from about 20, 30, 50, 80 or 100 μ l. Larger or small volumes may be used, as necessary, and it may be possible to achieve high throughput analysis using them. The entire affinity chromatography procedure may be automated by assembling the micro-columns into an array (e.g. with 96 micro-column arrays).

A variety of materials may be used as the source of potential interacting proteins. In one embodiment, a cellular extract or extracellular fluid may be used. The choice of starting material for the extract may be based upon the cell or tissue type or type of fluid that would be expected to contain proteins that interact with the target protein. Micro-organisms or other organisms are grown in a medium that is appropriate for that organism and can be grown in specific conditions to promote the expression of proteins that may interact with the target protein. Exemplary starting material that may be used to make a suitable extract are: 1) one or more types of tissue derived from an animal, plant, or other multi-cellular organism, 2) cells grown in tissue culture that were derived from an animal or human, plant or other source, 3) micro-organisms grown in suspension or non-suspension cultures, 4) virus-infected cells, 5) purified organelles (including, but not restricted to nuclei, mitochondria, membranes, Golgi, endoplasmic reticulum, lysosomes, or peroxisomes) prepared by differential centrifugation or another procedure from animal, plant or other kinds of eukaryotic cells, 6) serum or other bodily fluids including, but not limited to, blood, urine, semen, synovial fluid, cerebrospinal fluid, amniotic fluid, lymphatic fluid or interstitial fluid. In other embodiments, a total cell extract may not be the optimal source of interacting proteins. For example, if the ligand is known to act in the nucleus, a nuclear extract can provide a 10-fold enrichment of proteins that are likely to interact with the ligand. In addition, proteins that are present in the extract in low

concentrations may be enriched using another chromatographic method to fractionate the extract before screening various pools for an interacting protein.

Extracts are prepared by methods known to those of skill in the art. The extracts may be prepared at a low temperature (e.g., 4°C) in order to retard denaturation or degradation of proteins in the extract. The pH of the extract may be adjusted to be appropriate for the body fluid or tissue, cellular, or organellar source that is used for the procedure (e.g. pH 7-8 for cytosolic extracts from mammals, but low pH for lysosomal extracts). The concentration of chaotropic or non-chaotropic salts in the extracting solution may be adjusted so as to extract the appropriate sets of proteins for the procedure. Glycerol may be added to the extract, as it aids in maintaining the stability of many proteins and also reduces background non-specific binding. Both the lysis buffer and column buffer may contain protease inhibitors to minimize proteolytic degradation of proteins in the extract and to protect the polypeptide. Appropriate co-factors that could potentially interact with the interacting proteins may be added to the extracting solution. One or more nucleases or another reagent may be added to the extract, if appropriate, to prevent protein-protein interactions that are mediated by nucleic acids. Appropriate detergents or other agents may be added to the solution, if desired, to extract membrane proteins from the cells or tissue. A reducing agent (e.g. dithiothreitol or 2-mercaptoethanol or glutathione or other agent) may be added. Trace metals or a chelating agent may be added, if desired, to the extracting solution.

Usually, the extract is centrifuged in a centrifuge or ultracentrifuge or filtered to provide a clarified supernatant solution. This supernatant solution may be dialyzed using dialysis tubing, or another kind of device that is standard in the art, against a solution that is similar to, but may not be identical with, the solution that was used to make the extract. The extract is clarified by centrifugation or filtration again immediately prior to its use in affinity chromatography.

In some cases, the crude lysate will contain small molecules that can interfere with the affinity chromatography. This can be remedied by precipitating proteins with ammonium sulfate, centrifugation of the precipitate, and re-suspending the proteins in the affinity column buffer followed by dialysis. An additional centrifugation of the sample may be needed to remove any particulate matter prior to application to the affinity columns.

The amount of cell extract applied to the column may be important for any embodiment. If too little extract is applied to the column and the interacting protein is

present at low concentration, the level of interacting protein retained by the column may be difficult to detect. Conversely, if too much extract is applied to the column, protein may precipitate on the column or competition by abundant interacting proteins for the limited amount of protein ligand may result in a difficulty in detecting minor species.

5 The columns functionalized with a polypeptide of the invention are loaded with protein extract from an appropriate source that has been dialyzed against a buffer that is consistent with the nature of the expected interaction. The pH, salt concentrations and the presence or absence of reducing and chelating agents, trace metals, detergents, and co-factors may be adjusted according to the nature of the expected interaction. Most
10 commonly, the pH and the ionic strength are chosen so as to be close to physiological for the source of the extract. The extract is most commonly loaded under gravity onto the columns at a flow rate of about 4-6 column volumes per hour, but this flow rate can be adjusted for particular circumstances in an automated procedure.

15 The volume of the extract that is loaded on the columns can be varied but is most commonly equivalent to about 5 to 10 column volumes. When large volumes of extract are loaded on the columns, there is often an improvement in the signal-to-noise ratio because more protein from the extract is available to bind to the protein ligand, whereas the background binding of proteins from the extract to the solid support saturates with low amounts of extract.

20 A control column may be included that contains the highest concentration of protein ligand, but buffer rather than extract is loaded onto this column. The elutions (eluates) from this column will contain polypeptide that failed to be attached to the column in a covalent manner, but no proteins that are derived from the extract.

25 The columns may be washed with a buffer appropriate to the nature of the interaction being analyzed, usually, but not necessarily, the same as the loading buffer. An elution buffer with an appropriate pH, glycerol, and the presence or absence of reducing agent, chelating agent, cofactors, and detergents are all important considerations. The columns may be washed with anywhere from about 5 to 20 column volumes of each wash buffer to eliminate unbound proteins from the natural extract. The flow rate of the wash is
30 usually adjusted to about 4 to 6 column volumes per hour by using gravity or an automated procedure, but other flow rates are possible in specific circumstances.

 In order to elute the proteins that have been retained by the column, the interactions between the extract proteins and the column ligand should be disrupted. This is performed

by eluting the column with a solution of salt or detergent. Retention of activity by the eluted proteins may require the presence of glycerol and a buffer of appropriate pH, as well as proper choices of ionic strength and the presence or absence of appropriate reducing agent, chelating agent, trace metals, cofactors, detergents, chaotropic agents, and other reagents. If physical identification of the bound proteins is the objective, the elution may be performed sequentially, first with buffer of high ionic strength and then with buffer containing a protein denaturant, most commonly, but not restricted to sodium dodecyl sulfate (SDS), urea, or guanidine hydrochloride. In certain instances, the column is eluted with a protein denaturant, particularly SDS, for example as a 1% SDS solution. Using only the SDS wash, and omitting the salt wash, may result in SDS-gels that have higher resolution (sharper bands with less smearing). Also, using only the SDS wash results in half as many samples to analyze. The volume of the eluting solution may be varied but is normally about 2 to 4 column volumes. For 20 ml columns, the flow rate of the eluting procedures are most commonly about 4 to 6 column volumes per hour, under gravity, but can be varied in an automated procedure.

The proteins from the extract that were bound to S^6 and are eluted from the affinity columns may be most easily resolved for identification by an electrophoresis procedure, but this procedure may be modified, replaced by another suitable method, or omitted. Any of the denaturing or non-denaturing electrophoresis procedures that are standard in the art may be used for this purpose, including SDS-PAGE, gradient gels, capillary electrophoresis, and two-dimensional gels with isoelectric focusing in the first dimension and SDS-PAGE in the second. Typically, the individual components in the column eluent are separated by polyacrylamide gel electrophoresis.

After electrophoresis, protein bands or spots may be visualized using any number of methods known to those of skill in the art, including staining techniques such as Coomassie blue or silver staining, or some other agent that is standard in the art. Alternatively, autoradiography can be used for visualizing proteins isolated from organisms cultured on media containing a radioactive label, for example $^{35}\text{SO}_4^{2-}$ or $^{35}\text{[S]}$ methionine, that is incorporated into the proteins. The use of radioactively labeled extract allows a distinction to be made between extract proteins that were retained by the column and proteolytic fragments of the ligand that may be released from the column.

Protein bands that are derived from the extract (i.e. it did not elute from the control column that was not loaded with protein from the extract) and bound to an experimental

column that contained polypeptide covalently attached to the solid support, and did not bind to a control column that did not contain any polypeptide, may be excised from the stained electrophoretic gel and further characterized.

5 To identify the protein interactor by mass spectrometry, it may be desirable to reduce the disulfide bonds of the protein followed by alkylation of the free thiols prior to digestion of the protein with protease. The reduction may be performed by treatment of the gel slice with a reducing agent, for example with dithiothreitol, whereupon, the protein is alkylated by treating the gel slice with a suitable alkylating agent, for example iodoacetamide.

10 Prior to analysis by mass spectrometry, the protein may be chemically or enzymatically digested. The protein sample in the gel slice may be subjected to *in-gel* digestion. Shevchenko A. et al., Mass Spectrometric Sequencing of Proteins from Silver Stained Polyacrylamide Gels. Analytical Chemistry 1996, 58, 850-858. One method of digestion is by treatment with the enzyme trypsin. The resulting peptides are extracted
15 from the gel slice into a buffer.

The peptide fragments may be purified, for example by use of chromatography. A solid support that differentially binds the peptides and not the other compounds derived from the gel slice, the protease reaction or the peptide extract may be used. The peptides may be eluted from the solid support into a small volume of a solution that is compatible
20 with mass spectrometry (e.g. 50% acetonitrile/0.1% trifluoroacetic acid).

The preparation of a protein sample from a gel slice that is suitable for mass spectrometry may also be done by an automated procedure.

Peptide samples derived from gel slices may be analyzed by any one of a variety of techniques in mass spectrometry as further described above. This technique may be used to
25 assign function to an unknown protein based upon the known function of the interacting protein in the same or a homologous/orthologous organism.

Eluates from the affinity chromatography columns may also be analyzed directly without resolution by electrophoretic methods, by proteolytic digestion with a protease in solution, followed by applying the proteolytic digestion products to a reverse phase column
30 and eluting the peptides from the column.

In yet another embodiment, proteins that interact with a polypeptide of the invention may be identified using an interaction trap assay (see also, U.S. Patent NO: 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J Biol Chem* 268:12046-12054;

Bartel *et al.* (1993) *Biotechniques* 14:920-924; and Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696).

In another embodiment, a method of the present invention makes use of chimeric genes which express hybrid proteins. To illustrate, a first hybrid gene comprises the coding sequence for a DNA-binding domain of a transcriptional activator fused in frame to the coding sequence for a "bait" protein, e.g., a polypeptide of the invention of sufficient length to bind to a potential interacting protein. The second hybrid protein encodes a transcriptional activation domain fused in frame to a gene encoding a "fish" protein, e.g., a potential interacting protein of sufficient length to interact with a polypeptide of the invention portion of the bait fusion protein. If the bait and fish proteins are able to interact, e.g., form a protein-protein interaction, they bring into close proximity the two domains of the transcriptional activator. This proximity causes transcription of a reporter gene which is operably linked to a transcriptional regulatory site responsive to the transcriptional activator, and expression of the reporter gene can be detected and used to score for the interaction of the bait and fish proteins.

In accordance with the present invention, the method includes providing a host cell, typically a yeast cell, e.g., *Kluyverei lactis*, *Schizosaccharomyces pombe*, *Ustilago maydis*, *Saccharomyces cerevisiae*, *Neurospora crassa*, *Aspergillus niger*, *Aspergillus nidulans*, *Pichia pastoris*, *Candida tropicalis*, and *Hansenula polymorpha*, though most preferably *S. cerevisiae* or *S. pombe*. The host cell contains a reporter gene having a binding site for the DNA-binding domain of a transcriptional activator used in the bait protein, such that the reporter gene expresses a detectable gene product when the gene is transcriptionally activated. The first chimeric gene may be present in a chromosome of the host cell, or as part of an expression vector.

The host cell also contains a first chimeric gene which is capable of being expressed in the host cell. The gene encodes a chimeric protein, which comprises (a) a DNA-binding domain that recognizes the responsive element on the reporter gene in the host cell, and (b) a bait protein (e.g., a polypeptide of the invention).

A second chimeric gene is also provided which is capable of being expressed in the host cell, and encodes the "fish" fusion protein. In one embodiment, both the first and the second chimeric genes are introduced into the host cell in the form of plasmids. Preferably, however, the first chimeric gene is present in a chromosome of the host cell and the second chimeric gene is introduced into the host cell as part of a plasmid.

The DNA-binding domain of the first hybrid protein and the transcriptional activation domain of the second hybrid protein may be derived from transcriptional activators having separable DNA-binding and transcriptional activation domains. For instance, these separate DNA-binding and transcriptional activation domains are known to
5 be found in the yeast GAL4 protein, and are known to be found in the yeast GCN4 and ADR1 proteins. Many other proteins involved in transcription also have separable binding and transcriptional activation domains which make them useful for the present invention, and include, for example, the LexA and VP16 proteins. It will be understood that other (substantially) transcriptionally-inert DNA-binding domains may be used in the subject
10 constructs; such as domains of ACE1, λ cI, lac repressor, jun or fos. In another embodiment, the DNA-binding domain and the transcriptional activation domain may be from different proteins. The use of a LexA DNA binding domain provides certain advantages. For example, in yeast, the LexA moiety contains no activation function and has no known affect on transcription of yeast genes. In addition, use of LexA allows
15 control over the sensitivity of the assay to the level of interaction (see, for example, the Brent *et al.* PCT publication WO94/10300).

In certain embodiments, any enzymatic activity associated with the bait or fish proteins is inactivated, e.g., dominant negative or other mutants of a protein-protein interaction component can be used.

20 Continuing with the illustrative example, a polypeptide of the invention-mediated interaction, if any, between the bait and fish fusion proteins in the host cell, causes the activation domain to activate transcription of the reporter gene. The method is carried out by introducing the first chimeric gene and the second chimeric gene into the host cell, and subjecting that cell to conditions under which the bait and fish fusion proteins and are
25 expressed in sufficient quantity for the reporter gene to be activated. The formation of a protein complex containing a polypeptide of the invention results in a detectable signal produced by the expression of the reporter gene.

In still further embodiments, the protein-protein interaction of interest is generated in whole cells, taking advantage of cell culture techniques to support the subject assay. For
30 example, the protein-protein interaction of interest can be constituted in a prokaryotic or eukaryotic cell culture system. Advantages to generating the protein complex in an intact cell includes the ability to screen for inhibitors of the level or activity of the complex which are functional in an environment more closely approximating that which therapeutic use of

the inhibitor would require, including the ability of the agent to gain entry into the cell. Furthermore, certain of the *in vivo* embodiments of the assay are amenable to high throughput analysis of candidate agents.

5 The components of the protein complex comprising a polypeptide of the invention can be endogenous to the cell selected to support the assay. Alternatively, some or all of the components can be derived from exogenous sources. For instance, fusion proteins can be introduced into the cell by recombinant techniques (such as through the use of an expression vector), as well as by microinjecting the fusion protein itself or mRNA encoding the fusion protein. Moreover, in the whole cell embodiments of the subject assay, the
10 reporter gene construct can provide, upon expression, a selectable marker. Such embodiments of the subject assay are particularly amenable to high through-put analysis in that proliferation of the cell can provide a simple measure of the protein-protein interaction.

The amount of transcription from the reporter gene may be measured using any method known to those of skill in the art to be suitable. For example, specific mRNA
15 expression may be detected using Northern blots or specific protein product may be identified by a characteristic stain, western blots or an intrinsic activity. In certain embodiments, the product of the reporter gene is detected by an intrinsic activity associated with that product. For instance, the reporter gene may encode a gene product that, by enzymatic activity, gives rise to a detection signal based on color, fluorescence, or
20 luminescence.

The interaction trap assay of the invention may also be used to identify test agents capable of modulating formation of a complex comprising a polypeptide of the invention. In general, the amount of expression from the reporter gene in the presence of the test compound is compared to the amount of expression in the same cell in the absence of the
25 test compound. Alternatively, the amount of expression from the reporter gene in the presence of the test compound may be compared with the amount of transcription in a substantially identical cell that lacks a component of the protein-protein interaction involving a polypeptide of the invention.

30 7. Antibodies

Another aspect of the invention pertains to antibodies specifically reactive with a polypeptide of the invention. For example, by using peptides based on a polypeptide of the invention, e.g., having an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 or an

immunogenic fragment thereof, antisera or monoclonal antibodies may be made using standard methods. An exemplary immunogenic fragment may contain eight, ten or more consecutive amino acid residues of SEQ ID NO: 2 or SEQ ID NO: 4. Certain fragments that are predicted to be immunogenic for the subject amino acid sequences (predicted) are set forth in Table 2 contained in FIGURE 7

The term "antibody" as used herein is intended to include fragments thereof which are also specifically reactive with a polypeptide of the invention. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as is suitable for whole antibodies. For example, F(ab')₂ fragments can be generated by treating antibody with pepsin. The resulting F(ab')₂ fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules, as well as single chain (scFv) antibodies. Also within the scope of the invention are trimeric antibodies, humanized antibodies, human antibodies, and single chain antibodies. All of these modified forms of antibodies as well as fragments of antibodies are intended to be included in the term "antibody".

In one aspect, the present invention contemplates a purified antibody that binds specifically to a polypeptide of the invention and which does not substantially cross-react with a protein which is less than about 80%, or less than about 90%, identical to SEQ ID NO: 2 or SEQ ID NO: 4. In another aspect, the present invention contemplates an array comprising a substrate having a plurality of address, wherein at least one of the addresses has disposed thereon a purified antibody that binds specifically to a polypeptide of the invention.

Antibodies may be elicited by methods known in the art. For example, a mammal such as a mouse, a hamster or rabbit may be immunized with an immunogenic form of a polypeptide of the invention (e.g., an antigenic fragment which is capable of eliciting an antibody response). Alternatively, immunization may occur by using a nucleic acid of the acid, which presumably *in vivo* expresses the polypeptide of the invention giving rise to the immunogenic response observed. Techniques for conferring immunogenicity on a protein or peptide include conjugation to carriers or other techniques well known in the art. For instance, a peptidyl portion of a polypeptide of the invention may be administered in the presence of adjuvant. The progress of immunization may be monitored by detection of

antibody titers in plasma or serum. Standard ELISA or other immunoassays may be used with the immunogen as antigen to assess the levels of antibodies.

Following immunization, antisera reactive with a polypeptide of the invention may be obtained and, if desired, polyclonal antibodies isolated from the serum. To produce
5 monoclonal antibodies, antibody producing cells (lymphocytes) may be harvested from an immunized animal and fused by standard somatic cell fusion procedures with immortalizing cells such as myeloma cells to yield hybridoma cells. Such techniques are well known in the art, and include, for example, the hybridoma technique (originally developed by Kohler and Milstein, (1975) *Nature*, 256: 495-497), as the human B cell hybridoma technique
10 (Kozbar et al., (1983) *Immunology Today*, 4: 72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., (1985) *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. pp. 77-96). Hybridoma cells can be screened immunochemically for production of antibodies specifically reactive with the polypeptides of the invention and the monoclonal antibodies isolated.

15 Antibodies directed against the polypeptides of the invention can be used to selectively block the action of the polypeptides of the invention. Antibodies against a polypeptide of the invention may be employed to treat infections, particularly bacterial infections and diseases. For example, the present invention contemplates a method for treating a subject suffering from a *E. faecalis* related disease or disorder, comprising
20 administering to an animal having the condition a therapeutically effective amount of a purified antibody that binds specifically to a polypeptide of the invention. In another example, the present invention contemplates a method for inhibiting SEQ ID NO: 2 or SEQ ID NO: 4 dependent growth or infectivity of *E. faecalis*, comprising contacting *E. faecalis* with a purified antibody that binds specifically to a polypeptide of the invention.

25 In one embodiment, antibodies reactive with a polypeptide of the invention are used in the immunological screening of cDNA libraries constructed in expression vectors, such as λ gt11, λ gt18-23, λ ZAP, and λ ORF8. Messenger libraries of this type, having coding sequences inserted in the correct reading frame and orientation, can produce fusion proteins. For instance, λ gt11 will produce fusion proteins whose amino termini consist of
30 β -galactosidase amino acid sequences and whose carboxy termini consist of a foreign polypeptide. Antigenic epitopes of a polypeptide of the invention can then be detected with antibodies, as, for example, reacting nitrocellulose filters lifted from phage infected bacterial plates with an antibody specific for a polypeptide of the invention. Phage scored

by this assay can then be isolated from the infected plate. Thus, homologs of a polypeptide of the invention can be detected and cloned from other sources.

Antibodies may be employed to isolate or to identify clones expressing the polypeptides to purify the polypeptides by affinity chromatography.

5 In other embodiments, the polypeptides of the invention may be modified so as to increase their immunogenicity. For example, a polypeptide, such as an antigenically or immunologically equivalent derivative, may be associated, for example by conjugation, with an immunogenic carrier protein for example bovine serum albumin (BSA) or keyhole limpet haemocyanin (KLH). Alternatively a multiple antigenic peptide comprising multiple
10 copies of the protein or polypeptide, or an antigenically or immunologically equivalent polypeptide thereof may be sufficiently antigenic to improve immunogenicity so as to obviate the use of a carrier.

In other embodiments, the antibodies of the invention, or variants thereof, are modified to make them less immunogenic when administered to a subject. For example, if
15 the subject is human, the antibody may be "humanized"; where the complementarity determining region(s) of the hybridoma-derived antibody has been transplanted into a human monoclonal antibody, for example as described in Jones, P. et al. (1986), Nature 321, 522-525 or Tempest et al. (1991) Biotechnology 9, 266-273. Also, transgenic mice, or other mammals, may be used to express humanized antibodies. Such humanization may be
20 partial or complete.

The use of a nucleic acid of the invention in genetic immunization may employ a suitable delivery method such as direct injection of plasmid DNA into muscles (Wolff et al., Hum Mol Genet 1992, 1:363, Manthorpe et al., Hum. Gene Ther. 1993:4, 419), delivery of DNA complexed with specific protein carriers (Wu et al., J Biol Chem. 1989: 264,16985), coprecipitation of DNA with calcium phosphate (Benvenisty & Reshef, PNAS
25 USA, 1986:83,9551), encapsulation of DNA in various forms of liposomes (Kaneda et al., Science 1989:243,375), particle bombardment (Tang et al., Nature 1992, 356:152, Eisenbraun et al., DNA Cell Biol 1993, 12:791) and *in vivo* infection using cloned retroviral vectors (Seeger et al., PNAS USA 1984:81,5849).

30

8. Diagnostic Assays

The invention further provides a method for detecting the presence of *E. faecalis* in a biological sample. Detection of *E. faecalis* in a subject, particularly a mammal, and

especially a human, will provide a diagnostic method for diagnosis of a *E. faecalis* related disease or disorder. In general, the method involves contacting the biological sample with a compound or an agent capable of detecting a polypeptide of the invention or a nucleic acid of the invention. The term "biological sample" when used in reference to a diagnostic assay is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

The detection method of the invention may be used to detect the presence of *E. faecalis* in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of a nucleic acid of the invention include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of polypeptides of the invention include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunofluorescence, radioimmunoassays and competitive binding assays. Alternatively, polypeptides of the invention can be detected *in vivo* in a subject by introducing into the subject a labeled antibody specific for a polypeptide of the invention. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. It may be possible to use all of the diagnostic methods disclosed herein for pathogens in addition to *E. faecalis*.

Nucleic acids for diagnosis may be obtained from an infected individual's cells and tissues, such as bone, blood, muscle, cartilage, and skin. Nucleic acids, e.g., DNA and RNA, may be used directly for detection or may be amplified, e.g., enzymatically by using PCR or other amplification technique, prior to analysis. Using amplification, characterization of the species and strain of prokaryote present in an individual, may be made by an analysis of the genotype of the prokaryote gene. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the genotype of a reference sequence. Point mutations can be identified by hybridizing a nucleic acid, e.g., amplified DNA, to a nucleic acid of the invention, which nucleic acid may be labeled. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in the electrophoretic mobility of the DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing. See, e.g. Myers et al., Science, 230: 1242 (1985). Sequence changes at specific locations also may be revealed by nuclease protection assays, such as RNase and S1 protection or a chemical cleavage method. See, e.g., Cotton et al., Proc. Natl. Acad. Sci., USA, 85: 4397-4401 (1985).

Agents for detecting a nucleic acid of the invention, e.g., comprising the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3, include labeled or labelable nucleic acid probes capable of hybridizing to a nucleic acid of the invention. The nucleic acid probe can comprise, for example, the full length sequence of a nucleic acid of the invention, or an equivalent thereof, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 3, or the complement thereof. Agents for detecting a polypeptide of the invention, e.g., comprising an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, include labeled or labelable antibodies capable of binding to a polypeptide of the invention. Antibodies may be polyclonal, or alternatively, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or F(ab')₂) can be used. Labeling the probe or antibody also encompasses direct labeling of the probe or antibody by coupling (e.g., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

In certain embodiments, detection of a nucleic acid of the invention in a biological sample involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Pat. Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran et al. (1988) Science 241:1077-1080; and Nakazawa et al. (1994) PNAS 91:360-364), the latter of which can be particularly useful for distinguishing between orthologs of polynucleotides of the invention (see Abravaya et al. (1995) Nucleic Acids Res. 23:675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a nucleic acid of the invention under conditions such that hybridization and amplification of the polynucleotide (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample.

In one aspect, the present invention contemplates a method for detecting the presence of *E. faecalis* in a sample, the method comprising: (a) providing a sample to be tested for the presence of *E. faecalis*; (b) contacting the sample with an antibody reactive

against eight consecutive amino acid residues of SEQ ID NO: 2 or SEQ ID NO: 4 under conditions which permit association between the antibody and its ligand; and (c) detecting interaction of the antibody with its ligand, thereby detecting the presence of *E. faecalis* in the sample.

5 In another aspect, the present invention contemplates a method for detecting the presence of *E. faecalis* in a sample, the method comprising: (a) providing a sample to be tested for the presence of *E. faecalis*; (b) contacting the sample with an antibody that binds specifically to a polypeptide of the invention under conditions which permit association between the antibody and its ligand; and (c) detecting interaction of the antibody with its
10 ligand, thereby detecting the presence of *E. faecalis* in the sample.

 In yet another example, the present invention contemplates a method for diagnosing a patient suffering from a *E. faecalis* related disease or disorder, comprising: (a) obtaining a biological sample from a patient; (b) detecting the presence or absence of a polypeptide of the invention, or a nucleic acid encoding a polypeptide of the invention, in the sample; and
15 (c) diagnosing a patient suffering from a *E. faecalis* related disease or disorder based on the presence of a polypeptide of the invention, or a nucleic acid encoding a polypeptide of the invention, in the patient sample.

 The diagnostic assays of the invention may also be used to monitor the effectiveness of an anti-*E. faecalis* treatment in an individual suffering from an *E. faecalis* related disease
20 or disorder. For example, the presence and/or amount of a nucleic acid of the invention or a polypeptide of the invention can be detected in an individual suffering from an *E. faecalis* related disease or disorder before and after treatment with anti-*E. faecalis* therapeutic agent. Any change in the level of a polynucleotide or polypeptide of the invention after treatment of the individual with the therapeutic agent can provide information about the effectiveness
25 of the treatment course. In particular, no change, or a decrease, in the level of a polynucleotide or polypeptide of the invention present in the biological sample will indicate that the therapeutic is successfully combating the *E. faecalis* related disease or disorder.

 The invention also encompasses kits for detecting the presence of *E. faecalis* in a biological sample. For example, the kit can comprise a labeled or labelable compound or
30 agent capable of detecting a polynucleotide or polypeptide of the invention in a biological sample; means for determining the amount of *E. faecalis* in the sample; and means for comparing the amount of *E. faecalis* in the sample with a standard. The compound or agent

can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect a polynucleotide or polypeptide of the invention.

9. Drug Discovery

5 Modulators to polypeptides of the invention and other structurally related molecules, and complexes containing the same, may be identified and developed as set forth below and otherwise using techniques and methods known to those of skill in the art. The modulators of the invention may be employed, for instance, to inhibit and treat *E. faecalis* associated diseases or conditions, such as urinary tract infection, surgical wound
10 infection, bacteremia, intra abdominal infection, pelvic infection, central nervous system infection, osteomyelitis, pulmonary infection, and endocarditis.

 A variety of methods for inhibiting the growth or infectivity of *E. faecalis* are contemplated by the present invention. For example, exemplary methods involve contacting *E. faecalis* with a polypeptide of the invention that modulates the same or
15 another polypeptide from such pathogen, a nucleic acid encoding such polypeptide of the invention, or a compound thought or shown to be effective against such pathogen.

 For example, in one aspect, the present invention contemplates a method for treating a patient suffering from an infection of *E. faecalis*, comprising administering to the patient an amount of a SEQ ID NO: 2 or SEQ ID NO: 4 inhibitor effective to inhibit the expression
20 and/or activity of a polypeptide of the invention. In certain instances, the animal is a human or a livestock animal such as a cow, pig, goat or sheep. The present invention further contemplates a method for treating a subject suffering from a *E. faecalis* related disease or disorder, comprising administering to an animal having the condition a therapeutically effective amount of a molecule identified using one of the methods of the present invention.

25 The present invention contemplates making any molecule that is shown to modulate the activity of a polypeptide of the invention.

 In another embodiment, inhibitors, modulators of the subject polypeptides, or biological complexes containing them, may be used in the manufacture of a medicament for any number of uses, including, for example, treating any disease or other treatable condition
30 of a patient (including humans and animals), and particularly a disease caused by *E. faecalis*, such as, for example, one of the following: urinary tract infection, surgical wound infection, bacteremia, intra abdominal infection, pelvic infection, central nervous system infection, osteomyelitis, pulmonary infection, and endocarditis.

(a) *Drug Design*

A number of techniques can be used to screen, identify, select and design chemical entities capable of associating with polypeptides of the invention, structurally homologous molecules, and other molecules. Knowledge of the structure for a polypeptide of the invention, determined in accordance with the methods described herein, permits the design and/or identification of molecules and/or other modulators which have a shape complementary to the conformation of a polypeptide of the invention, or more particularly, a druggable region thereof. It is understood that such techniques and methods may use, in addition to the exact structural coordinates and other information for a polypeptide of the invention, structural equivalents thereof described above (including, for example, those structural coordinates that are derived from the structural coordinates of amino acids contained in a druggable region as described above).

The term "chemical entity," as used herein, refers to chemical compounds, complexes of two or more chemical compounds, and fragments of such compounds or complexes. In certain instances, it is desirable to use chemical entities exhibiting a wide range of structural and functional diversity, such as compounds exhibiting different shapes (e.g., flat aromatic rings(s), puckered aliphatic rings(s), straight and branched chain aliphatics with single, double, or triple bonds) and diverse functional groups (e.g., carboxylic acids, esters, ethers, amines, aldehydes, ketones, and various heterocyclic rings).

In one aspect, the method of drug design generally includes computationally evaluating the potential of a selected chemical entity to associate with any of the molecules or complexes of the present invention (or portions thereof). For example, this method may include the steps of (a) employing computational means to perform a fitting operation between the selected chemical entity and a druggable region of the molecule or complex; and (b) analyzing the results of said fitting operation to quantify the association between the chemical entity and the druggable region.

A chemical entity may be examined either through visual inspection or through the use of computer modeling using a docking program such as GRAM, DOCK, or AUTODOCK (Dunbrack et al., *Folding & Design*, 2:27-42 (1997)). This procedure can include computer fitting of chemical entities to a target to ascertain how well the shape and the chemical structure of each chemical entity will complement or interfere with the structure of the subject polypeptide (Bugg et al., *Scientific American*, Dec.: 92-98 (1993); West et al., *TIPS*, 16:67-74 (1995)). Computer programs may also be employed to estimate

the attraction, repulsion, and steric hindrance of the chemical entity to a druggable region, for example. Generally, the tighter the fit (e.g., the lower the steric hindrance, and/or the greater the attractive force) the more potent the chemical entity will be because these properties are consistent with a tighter binding constant. Furthermore, the more specificity
5 in the design of a chemical entity the more likely that the chemical entity will not interfere with related proteins, which may minimize potential side-effects due to unwanted interactions.

A variety of computational methods for molecular design, in which the steric and electronic properties of druggable regions are used to guide the design of chemical entities,
10 are known: Cohen et al. (1990) *J. Med. Cam.* 33: 883-894; Kuntz et al. (1982) *J. Mol. Biol* 161: 269-288; DesJarlais (1988) *J. Med. Cam.* 31: 722-729; Bartlett et al. (1989) *Spec. Publ., Roy. Soc. Chem.* 78: 182-196; Goodford et al. (1985) *J. Med. Cam.* 28: 849-857; and DesJarlais et al. *J. Med. Cam.* 29: 2149-2153. Directed methods generally fall into two categories: (1) design by analogy in which 3-D structures of known chemical entities (such as
15 from a crystallographic database) are docked to the druggable region and scored for goodness-of-fit; and (2) *de novo* design, in which the chemical entity is constructed piece-wise in the druggable region. The chemical entity may be screened as part of a library or a database of molecules. Databases which may be used include ACD (Molecular Designs Limited), NCI (National Cancer Institute), CCDC (Cambridge Crystallographic Data Center), CAST
20 (Chemical Abstract Service), Derwent (Derwent Information Limited), Maybridge (Maybridge Chemical Company Ltd), Aldrich (Aldrich Chemical Company), DOCK (University of California in San Francisco), and the Directory of Natural Products (Chapman & Hall). Computer programs such as CONCORD (Tripos Associates) or DB-Converter (Molecular Simulations Limited) can be used to convert a data set represented in
25 two dimensions to one represented in three dimensions.

Chemical entities may be tested for their capacity to fit spatially with a druggable region or other portion of a target protein. As used herein, the term "fits spatially" means that the three-dimensional structure of the chemical entity is accommodated geometrically by a druggable region. A favorable geometric fit occurs when the surface area of the
30 chemical entity is in close proximity with the surface area of the druggable region without forming unfavorable interactions. A favorable complementary interaction occurs where the chemical entity interacts by hydrophobic, aromatic, ionic, dipolar, or hydrogen donating

and accepting forces. Unfavorable interactions may be steric hindrance between atoms in the chemical entity and atoms in the druggable region.

If a model of the present invention is a computer model, the chemical entities may be positioned in a druggable region through computational docking. If, on the other hand,
5 the model of the present invention is a structural model, the chemical entities may be positioned in the druggable region by, for example, manual docking. As used herein the term "docking" refers to a process of placing a chemical entity in close proximity with a druggable region, or a process of finding low energy conformations of a chemical entity/druggable region complex.

10 In an illustrative embodiment, the design of potential modulator begins from the general perspective of shape complimentary for the druggable region of a polypeptide of the invention, and a search algorithm is employed which is capable of scanning a database of small molecules of known three-dimensional structure for chemical entities which fit geometrically with the target druggable region. Most algorithms of this type provide a
15 method for finding a wide assortment of chemical entities that are complementary to the shape of a druggable region of the subject polypeptide. Each of a set of chemical entities from a particular data-base, such as the Cambridge Crystallographic Data Bank (CCDB) (Allen et al. (1973) *J. Chem. Doc.* 13: 119), is individually docked to the druggable region of a polypeptide of the invention in a number of geometrically permissible orientations with
20 use of a docking algorithm. In certain embodiments, a set of computer algorithms called DOCK, can be used to characterize the shape of invaginations and grooves that form the active sites and recognition surfaces of the druggable region (Kuntz et al. (1982) *J. Mol. Biol.* 161: 269-288). The program can also search a database of small molecules for templates whose shapes are complementary to particular binding sites of a polypeptide of
25 the invention (DesJarlais et al. (1988) *J Med Chem* 31: 722-729).

The orientations are evaluated for goodness-of-fit and the best are kept for further examination using molecular mechanics programs, such as AMBER or CHARMM. Such algorithms have previously proven successful in finding a variety of chemical entities that are complementary in shape to a druggable region.

30 Goodford (1985, *J Med Chem* 28:849-857) and Boobbyer et al. (1989, *J Med Chem* 32:1083-1094) have produced a computer program (GRID) which seeks to determine regions of high affinity for different chemical groups (termed probes) of the druggable region. GRID hence provides a tool for suggesting modifications to known chemical entities that might

enhance binding. It may be anticipated that some of the sites discerned by GRID as regions of high affinity correspond to "pharmacophoric patterns" determined inferentially from a series of known ligands. As used herein, a "pharmacophoric pattern" is a geometric arrangement of features of chemical entities that is believed to be important for binding. Attempts have been
5 made to use pharmacophoric patterns as a search screen for novel ligands (Jakes et al. (1987) *J Mol Graph* 5:41-48; Brint et al. (1987) *J Mol Graph* 5:49-56; Jakes et al. (1986) *J Mol Graph* 4:12-20).

Yet a further embodiment of the present invention utilizes a computer algorithm such as CLIX which searches such databases as CCDB for chemical entities which can be oriented
10 with the druggable region in a way that is both sterically acceptable and has a high likelihood of achieving favorable chemical interactions between the chemical entity and the surrounding amino acid residues. The method is based on characterizing the region in terms of an ensemble of favorable binding positions for different chemical groups and then searching for orientations of the chemical entities that cause maximum spatial coincidence of individual
15 candidate chemical groups with members of the ensemble. The algorithmic details of CLIX is described in Lawrence et al. (1992) *Proteins* 12:31-41.

In this way, the efficiency with which a chemical entity may bind to or interfere with a druggable region may be tested and optimized by computational evaluation. For example, for a favorable association with a druggable region, a chemical entity must
20 preferably demonstrate a relatively small difference in energy between its bound and free states (i.e., a small deformation energy of binding). Thus, certain, more desirable chemical entities will be designed with a deformation energy of binding of not greater than about 10 kcal/mole, and more preferably, not greater than 7 kcal/mole. Chemical entities may interact with a druggable region in more than one conformation that is similar in overall
25 binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free entity and the average energy of the conformations observed when the chemical entity binds to the target.

In this way, the present invention provides computer-assisted methods for identifying or designing a potential modulator of the activity of a polypeptide of the invention including: supplying a computer modeling application with a set of structure
30 coordinates of a molecule or complex, the molecule or complex including at least a portion of a druggable region from a polypeptide of the invention; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

determining whether the chemical entity is expected to bind to the molecule or complex, wherein binding to the molecule or complex is indicative of potential modulation of the activity of a polypeptide of the invention.

5 In another aspect, the present invention provides a computer-assisted method for identifying or designing a potential modulator to a polypeptide of the invention, supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least a portion of a druggable region of a polypeptide of the invention; supplying the computer modeling application with a set of structure coordinates for a chemical entity; evaluating the potential binding interactions
10 between the chemical entity and active site of the molecule or molecular complex; structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity, and determining whether the modified chemical entity is expected to bind to the molecule or complex, wherein binding to the molecule or complex is indicative of potential modulation of the polypeptide of the invention.

15 In one embodiment, a potential modulator can be obtained by screening a peptide library (Scott and Smith, Science, 249:386-390 (1990); Cwirla et al., Proc. Natl. Acad. Sci., 87:6378-6382 (1990); Devlin et al., Science, 249:404-406 (1990)). A potential modulator selected in this manner could then be systematically modified by computer modeling programs until one or more promising potential drugs are identified. Such analysis has
20 been shown to be effective in the development of HIV protease inhibitors (Lam et al., Science 263:380-384 (1994); Wlodawer et al., Ann. Rev. Biochem. 62:543-585 (1993); Appelt, Perspectives in Drug Discovery and Design 1:23-48 (1993); Erickson, Perspectives in Drug Discovery and Design 1:109-128 (1993)). Alternatively a potential modulator may be selected from a library of chemicals such as those that can be licensed from third parties,
25 such as chemical and pharmaceutical companies. A third alternative is to synthesize the potential modulator *de novo*.

For example, in certain embodiments, the present invention provides a method for making a potential modulator for a polypeptide of the invention, the method including synthesizing a chemical entity or a molecule containing the chemical entity to yield a
30 potential modulator of a polypeptide of the invention, the chemical entity having been identified during a computer-assisted process including supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex including at least one druggable region from a polypeptide of the invention;

supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind to the molecule or complex at the active site, wherein binding to the molecule or complex is indicative of potential modulation. This method may further include the steps of evaluating
5 the potential binding interactions between the chemical entity and the active site of the molecule or molecular complex and structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity, which steps may be repeated one or more times.

Once a potential modulator is identified, it can then be tested in any standard assay
10 for the macromolecule depending of course on the macromolecule, including in high throughput assays. Further refinements to the structure of the modulator will generally be necessary and can be made by the successive iterations of any and/or all of the steps provided by the particular screening assay, in particular further structural analysis by e.g., ¹⁵N NMR relaxation rate determinations or x-ray crystallography with the modulator bound
15 to the subject polypeptide. These studies may be performed in conjunction with biochemical assays.

Once identified, a potential modulator may be used as a model structure, and analogs to the compound can be obtained. The analogs are then screened for their ability to bind the subject polypeptide. An analog of the potential modulator might be chosen as a
20 modulator when it binds to the subject polypeptide with a higher binding affinity than the predecessor modulator.

In a related approach, iterative drug design is used to identify modulators of a target protein. Iterative drug design is a method for optimizing associations between a protein and a modulator by determining and evaluating the three dimensional structures of successive
25 sets of protein/modulator complexes. In iterative drug design, crystals of a series of protein/modulator complexes are obtained and then the three-dimensional structures of each complex is solved. Such an approach provides insight into the association between the proteins and modulators of each complex. For example, this approach may be accomplished by selecting modulators with inhibitory activity, obtaining crystals of this
30 new protein/modulator complex, solving the three dimensional structure of the complex, and comparing the associations between the new protein/modulator complex and previously solved protein/modulator complexes. By observing how changes in the modulator affected the protein/modulator associations, these associations may be optimized.

In addition to designing and/or identifying a chemical entity to associate with a druggable region, as described above, the same techniques and methods may be used to design and/or identify chemical entities that either associate, or do not associate, with affinity regions, selectivity regions or undesired regions of protein targets. By such methods, selectivity for one or a few targets, or alternatively for multiple targets, from the same species or from multiple species, can be achieved.

For example, a chemical entity may be designed and/or identified for which the binding energy for one druggable region, e.g., an affinity region or selectivity region, is more favorable than that for another region, e.g., an undesired region, by about 20%, 30%, 50% to about 60% or more. It may be the case that the difference is observed between (a) more than two regions, (b) between different regions (selectivity, affinity or undesirable) from the same target, (c) between regions of different targets, (d) between regions of homologs from different species, or (e) between other combinations. Alternatively, the comparison may be made by reference to the K_d , usually the apparent K_d , of said chemical entity with the two or more regions in question.

In another aspect, prospective modulators are screened for binding to two nearby druggable regions on a target protein. For example, a modulator that binds a first region of a target polypeptide does not bind a second nearby region. Binding to the second region can be determined by monitoring changes in a different set of amide chemical shifts in either the original screen or a second screen conducted in the presence of a modulator (or potential modulator) for the first region. From an analysis of the chemical shift changes, the approximate location of a potential modulator for the second region is identified. Optimization of the second modulator for binding to the region is then carried out by screening structurally related compounds (e.g., analogs as described above). When modulators for the first region and the second region are identified, their location and orientation in the ternary complex can be determined experimentally. On the basis of this structural information, a linked compound, e.g., a consolidated modulator, is synthesized in which the modulator for the first region and the modulator for the second region are linked. In certain embodiments, the two modulators are covalently linked to form a consolidated modulator. This consolidated modulator may be tested to determine if it has a higher binding affinity for the target than either of the two individual modulators. A consolidated modulator is selected as a modulator when it has a higher binding affinity for the target than either of the two modulators. Larger consolidated modulators can be constructed in an

analogous manner, e.g., linking three modulators which bind to three nearby regions on the target to form a multilinked consolidated modulator that has an even higher affinity for the target than the linked modulator. In this example, it is assumed that is desirable to have the modulator bind to all the druggable regions. However, it may be the case that binding to
5 certain of the druggable regions is not desirable, so that the same techniques may be used to identify modulators and consolidated modulators that show increased specificity based on binding to at least one but not all druggable regions of a target.

The present invention provides a number of methods that use drug design as described above. For example, in one aspect, the present invention contemplates a method
10 for designing a candidate compound for screening for inhibitors of a polypeptide of the invention, the method comprising: (a) determining the three dimensional structure of a crystallized polypeptide of the invention or a fragment thereof; and (b) designing a candidate inhibitor based on the three dimensional structure of the crystallized polypeptide or fragment.

15 In another aspect, the present invention contemplates a method for identifying a potential inhibitor of a polypeptide of the invention, the method comprising: (a) providing the three-dimensional coordinates of a polypeptide of the invention or a fragment thereof; (b) identifying a druggable region of the polypeptide or fragment; and (c) selecting from a database at least one compound that comprises three dimensional coordinates which
20 indicate that the compound may bind the druggable region; (d) wherein the selected compound is a potential inhibitor of a polypeptide of the invention.

In another aspect, the present invention contemplates a method for identifying a potential modulator of a molecule comprising a druggable region similar to that of SEQ ID NO: 2 or SEQ ID NO: 4, the method comprising: (a) using the atomic coordinates of amino
25 acid residues from SEQ ID NO: 2 or SEQ ID NO: 4, or a fragment thereof, \pm a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Å, to generate a three-dimensional structure of a molecule comprising a druggable region that is a portion of SEQ ID NO: 2 or SEQ ID NO: 4; (b) employing the three dimensional structure to design or select the potential modulator; (c) synthesizing the modulator; and
30 (d) contacting the modulator with the molecule to determine the ability of the modulator to interact with the molecule.

In another aspect, the present invention contemplates an apparatus for determining whether a compound is a potential inhibitor of a polypeptide having SEQ ID NO: 2 or SEQ

ID NO: 4, the apparatus comprising: (a) a memory that comprises: (i) the three dimensional coordinates and identities of the atoms of a polypeptide of the invention or a fragment thereof that form a druggable site; and (ii) executable instructions; and (b) a processor that is capable of executing instructions to: (i) receive three-dimensional structural information
5 for a candidate compound; (ii) determine if the three-dimensional structure of the candidate compound is complementary to the structure of the interior of the druggable site; and (iii) output the results of the determination.

In another aspect, the present invention contemplates a method for designing a potential compound for the prevention or treatment of *E. faecalis* related disease or
10 disorder, the method comprising: (a) providing the three dimensional structure of a crystallized polypeptide of the invention, or a fragment thereof; (b) synthesizing a potential compound for the prevention or treatment of *E. faecalis* related disease or disorder based on the three dimensional structure of the crystallized polypeptide or fragment; (c) contacting a polypeptide of the present invention or an *E. faecalis* with the potential compound; and
15 (d) assaying the activity of a polypeptide of the present invention, wherein a change in the activity of the polypeptide indicates that the compound may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

In another aspect, the present invention contemplates a method for designing a potential compound for the prevention or treatment of *E. faecalis* related disease or
20 disorder, the method comprising: (a) providing structural information of a druggable region derived from NMR spectroscopy of a polypeptide of the invention, or a fragment thereof; (b) synthesizing a potential compound for the prevention or treatment of *E. faecalis* related disease or disorder based on the structural information; (c) contacting a polypeptide of the present invention or an *E. faecalis* with the potential compound; and (d) assaying the
25 activity of a polypeptide of the present invention, wherein a change in the activity of the polypeptide indicates that the compound may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

(b) In Vitro Assays

Polypeptides of the invention may be used to assess the activity of small molecules
30 and other modulators in *in vitro* assays. In one embodiment of such an assay, agents are identified which modulate the biological activity of a protein, protein-protein interaction of interest or protein complex, such as an enzymatic activity, binding to other cellular

components, cellular compartmentalization, signal transduction, and the like. In certain embodiments, the test agent is a small organic molecule.

Assays may employ kinetic or thermodynamic methodology using a wide variety of techniques including, but not limited to, microcalorimetry, circular dichroism, capillary
5 zone electrophoresis, nuclear magnetic resonance spectroscopy, fluorescence spectroscopy, and combinations thereof.

The invention also provides a method of screening compounds to identify those which modulate the action of polypeptides of the invention, or polynucleotides encoding the same. The method of screening may involve high-throughput techniques. For example,
10 to screen for modulators, a synthetic reaction mix, a cellular compartment, such as a membrane, cell envelope or cell wall, or a preparation of any thereof, comprising a polypeptide of the invention and a labeled substrate or ligand of such polypeptide is incubated in the absence or the presence of a candidate molecule that may be a modulator of a polypeptide of the invention. The ability of the candidate molecule to modulate a
15 polypeptide of the invention is reflected in decreased binding of the labeled ligand or decreased production of product from such substrate. Detection of the rate or level of production of product from substrate may be enhanced by using a reporter system. Reporter systems that may be useful in this regard include but are not limited to colorimetric labeled substrate converted into product, a reporter gene that is responsive to
20 changes in a nucleic acid of the invention or polypeptide activity, and binding assays known in the art.

Another example of an assay for a modulator of a polypeptide of the invention is a competitive assay that combines a polypeptide of the invention and a potential modulator with molecules that bind to a polypeptide of the invention, recombinant molecules that bind
25 to a polypeptide of the invention, natural substrates or ligands, or substrate or ligand mimetics, under appropriate conditions for a competitive inhibition assay. Polypeptides of the invention can be labeled, such as by radioactivity or a colorimetric compound, such that the number of molecules of a polypeptide of the invention bound to a binding molecule or converted to product can be determined accurately to assess the effectiveness of the
30 potential modulator.

A number of methods for identifying a molecule which modulates the activity of a polypeptide are known in the art. For example, in one such method, a subject polypeptide is contacted with a test compound, and the activity of the subject polypeptide in the

presence of the test compound is determined, wherein a change in the activity of the subject polypeptide is indicative that the test compound modulates the activity of the subject polypeptide. In certain instances, the test compound agonizes the activity of the subject polypeptide, and in other instances, the test compound antagonizes the activity of the subject polypeptide.

In another example, a compound which modulates SEQ ID NO: 2 or SEQ ID NO: 4 dependent growth or infectivity of *E. faecalis* may be identified by (a) contacting a polypeptide of the invention with a test compound; and (b) determining the activity of the polypeptide in the presence of the test compound, wherein a change in the activity of the polypeptide is indicative that the test compound may modulate the growth or infectivity of *E. faecalis*.

(c) In Vivo Assays

Animal models of bacterial infection and/or disease may be used as an *in vivo* assay for evaluating the effectiveness of a potential drug target in treating or preventing diseases or disorders. A number of suitable animal models are described briefly below, however, these models are only examples and modifications, or completely different animal models, may be used in accord with the methods of the invention.

(i) Mouse Soft Tissue Model

The mouse soft tissue infection model is a sensitive and effective method for measurement of bacterial proliferation. In these models (Vogelman et al., 1988, J. Infect. Dis. 157: 287-298) anesthetized mice are infected with the bacteria in the muscle of the hind thigh. The mice can be either chemically immune compromised (e.g., cytoxan treated at 125 mg/kg on days -4, -2, and 0) or immunocompetent. The dose of microbe necessary to cause an infection is variable and depends on the individual microbe, but commonly is on the order of 10^5 - 10^6 colony forming units per injection for bacteria. A variety of mouse strains are useful in this model although Swiss Webster and DBA2 lines are most commonly used. Once infected the animals are conscious and show no overt ill effects of the infections for approximately 12 hours. After that time virulent strains cause swelling of the thigh muscle, and the animals can become bacteremic within approximately 24 hours. This model most effectively measures proliferation of the microbe, and this proliferation is measured by sacrifice of the infected animal and counting colonies from homogenized thighs.

(ii) Diffusion Chamber Model

A second model useful for assessing the virulence of microbes is the diffusion chamber model (Malouin et al., 1990, Infect. Immun. 58: 1247-1253; Doy et al., 1980, J. Infect. Dis. 2: 39-51; Kelly et al., 1989, Infect. Immun. 57: 344-350. In this model rodents have a diffusion chamber surgically placed in the peritoneal cavity. The chamber consists of a polypropylene cylinder with semipermeable membranes covering the chamber ends. Diffusion of peritoneal fluid into and out of the chamber provides nutrients for the microbes. The progression of the "infection" may be followed by examining growth, the exoproduct production or RNA messages. The time experiments are done by sampling multiple chambers.

(iii) *Endocarditis Model*

For bacteria, an important animal model effective in assessing pathogenicity and virulence is the endocarditis model (J. Santoro and M. E. Levinson, 1978, Infect. Immun. 19: 915-918). A rat endocarditis model can be used to assess colonization, virulence and proliferation.

(iv) *Osteomyelitis Model*

A fourth model useful in the evaluation of pathogenesis is the osteomyelitis model (Spagnolo et al., 1993, Infect. Immun. 61: 5225-5230). Rabbits are used for these experiments. Anesthetized animals have a small segment of the tibia removed and microorganisms are microinjected into the wound. The excised bone segment is replaced and the progression of the disease is monitored. Clinical signs, particularly inflammation and swelling are monitored. Termination of the experiment allows histologic and pathologic examination of the infection site to complement the assessment procedure.

(v) *Murine Septic Arthritis Model*

A fifth model relevant to the study of microbial pathogenesis is a murine septic arthritis model (Abdelnour et al., 1993, Infect. Immun. 61: 3879-3885). In this model mice are infected intravenously and pathogenic organisms are found to cause inflammation in distal limb joints. Monitoring of the inflammation and comparison of inflammation vs. inocula allows assessment of the virulence of related strains.

(vi) *Bacterial Peritonitis Model*

Finally, bacterial peritonitis offers rapid and predictive data on the virulence of strains (M. G. Bergeron, 1978, Scand. J. Infect. Dis. Suppl. 14: 189-206; S. D. Davis, 1975, Antimicrob. Agents Chemother. 8: 50-53). Peritonitis in rodents, such as mice, can provide essential data on the importance of targets. The end point may be lethality or clinical signs

can be monitored. Variation in infection dose in comparison to outcome allows evaluation of the virulence of individual strains.

A variety of other *in vivo* models are available and may be used when appropriate for specific pathogens or specific test agents. For example, target organ recovery assays
5 (Gordee et al., 1984, J. Antibiotics 37:1054-1065; Bannatyne et al., 1992, Infect. 20:168-170) may be useful for fungi and for bacterial pathogens which are not acutely virulent to animals.

It is also relevant to note that the species of animal used for an infection model, and the specific genetic make-up of that animal, may contribute to the effective evaluation of
10 the effects of a particular test agent. For example, immuno-incompetent animals may, in some instances, be preferable to immuno-competent animals. For example, the action of a competent immune system may, to some degree, mask the effects of the test agent as compared to a similar infection in an immuno-incompetent animal. In addition, many opportunistic infections, in fact, occur in immuno-compromised patients, so modeling an
15 infection in a similar immunological environment is appropriate.

10. Vaccines

There are provided by the invention, products, compositions and methods for raising immunological response against a pathogen, especially *E. faecalis*. In one aspect, a
20 polypeptide of the invention or a nucleic acid of the invention, or an antigenic fragment thereof, may be administered to a subject, optionally with a booster, adjuvant, or other composition that stimulates immune responses.

Another aspect of the invention relates to a method for inducing an immunological response in an individual, particularly a mammal which comprises inoculating the
25 individual with a polypeptide of the invention and/or a nucleic acid of the invention, adequate to produce antibody and/or T cell immune response to protect said individual from infection, particularly bacterial infection and most particularly *E. faecalis* infection. Also provided are methods whereby such immunological response slows bacterial replication. Yet another aspect of the invention relates to a method of inducing immunological response
30 in an individual which comprises delivering to such individual a nucleic acid vector, sequence or ribozyme to direct expression of a polypeptide of the invention and/or a nucleic acid of the invention *in vivo* in order to induce an immunological response, such as, to produce antibody and/or T cell immune response, including, for example, cytokine-

producing T cells or cytotoxic T cells, to protect said individual, preferably a human, from disease, whether that disease is already established within the individual or not. One example of administering the gene is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a ribozyme, a
5 modified nucleic acid, a DNA/RNA hybrid, a DNA-protein complex or an RNA-protein complex.

A further aspect of the invention relates to an immunological composition that when introduced into an individual, preferably a human, capable of having induced within it an immunological response, induces an immunological response in such individual to a nucleic
10 acid of the invention and/or a polypeptide encoded therefrom, wherein the composition comprises a recombinant nucleic acid of the invention and/or polypeptide encoded therefrom and/or comprises DNA and/or RNA which encodes and expresses an antigen of said nucleic acid of the invention, polypeptide encoded therefrom, or other polypeptide of the invention. The immunological response may be used therapeutically or prophylactically
15 and may take the form of antibody immunity and/or cellular immunity, such as cellular immunity arising from CTL or CD4+T cells.

In another embodiment, the invention relates to compositions comprising a polypeptide of the invention and an adjuvant. The adjuvant can be any vehicle which would typically enhance the antigenicity of a polypeptide, e.g., minerals (for instance, alum,
20 aluminum hydroxide or aluminum phosphate), saponins complexed to membrane protein antigens (immune stimulating complexes), pluronic polymers with mineral oil, killed mycobacteria in mineral oil, Freund's complete adjuvant, bacterial products, such as muramyl dipeptide (MDP) and lipopolysaccharide (LPS), as well as lipid A, liposomes, or any of the other adjuvants known in the art. A polypeptide of the invention can be
25 emulsified with, absorbed onto, or coupled with the adjuvant.

A polypeptide of the invention may be fused with co-protein or chemical moiety which may or may not by itself produce antibodies, but which is capable of stabilizing the first protein and producing a fused or modified protein which will have antigenic and/or immunogenic properties, and preferably protective properties. Thus fused recombinant
30 protein, may further comprise an antigenic co-protein, such as lipoprotein D from *Hemophilus influenzae*, Glutathione-S-transferase (GST) or beta-galactosidase, or any other relatively large co-protein which solubilizes the protein and facilitates production and purification thereof. Moreover, the co-protein may act as an adjuvant in the sense of

providing a generalized stimulation of the immune system of the organism receiving the protein. The co-protein may be attached to either the amino- or carboxy-terminus of a polypeptide of the invention.

5 Provided by this invention are compositions, particularly vaccine compositions, and methods comprising the polypeptides and/or polynucleotides of the invention and immunostimulatory DNA sequences, such as those described in Sato, Y. et al. Science 273: 352 (1996).

10 Also, provided by this invention are methods using the described polynucleotide or particular fragments thereof, which have been shown to encode non-variable regions of bacterial cell surface proteins, in polynucleotide constructs used in such genetic immunization experiments in animal models of infection with *E. faecalis*. Such experiments will be particularly useful for identifying protein epitopes able to provoke a prophylactic or therapeutic immune response. It is believed that this approach will allow for the subsequent preparation of monoclonal antibodies of particular value, derived from
15 the requisite organ of the animal successfully resisting or clearing infection, for the development of prophylactic agents or therapeutic treatments of bacterial infection, particularly *E. faecalis* infection, in mammals, particularly humans.

A polypeptide of the invention may be used as an antigen for vaccination of a host to produce specific antibodies which protect against invasion of bacteria, for example by
20 blocking adherence of bacteria to damaged tissue.

11. Array Analysis

In part, the present invention is directed to the use of subject nucleic acids in arrays to assess gene expression. In another part, the present invention is directed to the use of
25 subject nucleic acids in arrays for *E. faecalis*. In yet another part, the present invention contemplates using the subject nucleic acids to interact with probes contained on arrays.

In one aspect, the present invention contemplates an array comprising a substrate having a plurality of addresses, wherein at least one of the addresses has disposed thereon a capture probe that can specifically bind to a nucleic acid of the invention. In another
30 aspect, the present invention contemplates a method for detecting expression of a nucleotide sequence which encodes a polypeptide of the invention, or a fragment thereof, using the foregoing array by: (a) providing a sample comprising at least one mRNA molecule; (b) exposing the sample to the array under conditions which promote

hybridization between the capture probe disposed on the array and a nucleic acid complementary thereto; and (c) detecting hybridization between an mRNA molecule of the sample and the capture probe disposed on the array, thereby detecting expression of a sequence which encodes for a polypeptide of the invention, or a fragment thereof.

5 Arrays are often divided into microarrays and macroarrays, where microarrays have a much higher density of individual probe species per area. Microarrays may have as many as 1000 or more different probes in a 1 cm² area. There is no concrete cut-off to demarcate the difference between micro- and macroarrays, and both types of arrays are contemplated for use with the invention.

10 Microarrays are known in the art and generally consist of a surface to which probes that correspond in sequence to gene products (e.g., cDNAs, mRNAs, oligonucleotides) are bound at known positions. In one embodiment, the microarray is an array (e.g., a matrix) in which each position represents a discrete binding site for a product encoded by a gene (e.g., a protein or RNA), and in which binding sites are present for products of most or almost all
15 of the genes in the organism's genome. In certain embodiments, the binding site or site is a nucleic acid or nucleic acid analogue to which a particular cognate cDNA can specifically hybridize. The nucleic acid or analogue of the binding site may be, e.g., a synthetic oligomer, a full-length cDNA, a less-than full length cDNA, or a gene fragment.

Although in certain embodiments the microarray contains binding sites for products
20 of all or almost all genes in the target organism's genome, such comprehensiveness is not necessarily required. Usually the microarray will have binding sites corresponding to at least 100, 500, 1000, 4000 genes or more. In certain embodiments, arrays will have anywhere from about 50, 60, 70, 80, 90, or even more than 95% of the genes of a particular organism represented. The microarray typically has binding sites for genes relevant to
25 testing and confirming a biological network model of interest. Several exemplary human microarrays are publicly available.

The probes to be affixed to the arrays are typically polynucleotides. These DNAs can be obtained by, e.g., polymerase chain reaction (PCR) amplification of gene segments from genomic DNA, cDNA (e.g., by RT-PCR), or cloned sequences. PCR primers are
30 chosen, based on the known sequence of the genes or cDNA, that result in amplification of unique fragments (e.g., fragments that do not share more than 10 bases of contiguous identical sequence with any other fragment on the microarray). Computer programs are useful in the design of primers with the required specificity and optimal amplification

properties. See, e.g., Oligo pl version 5.0 (National Biosciences). In an alternative embodiment, the binding (hybridization) sites are made from plasmid or phage clones of genes, cDNAs (e.g., expressed sequence tags), or inserts therefrom (Nguyen et al., 1995, *Genomics* 29:207-209).

5 A number of methods are known in the art for affixing the nucleic acids or analogues to a solid support that makes up the array (Schena et al., 1995, *Science* 270:467-470; DeRisi et al., 1996, *Nature Genetics* 14:457-460; Shalon et al., 1996, *Genome Res.* 6:639-645; and Schena et al., 1995, *Proc. Natl. Acad. Sci. USA* 93:10539-11286).

10 Another method for making microarrays is by making high-density oligonucleotide arrays (Fodor et al., 1991, *Science* 251:767-773; Pease et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:5022-5026; Lockhart et al., 1996, *Nature Biotech* 14:1675; U.S. Pat. Nos. 5,578,832; 5,556,752; and 5,510,270; Blanchard et al., 1996, 11: 687-90).

15 Other methods for making microarrays, e.g., by masking (Maskos and Southern, 1992, *Nuc. Acids Res.* 20:1679-1684), may also be used. In principal, any type of array, for example, dot blots on a nylon hybridization membrane (see Sambrook et al., *Molecular Cloning - A Laboratory Manual* (2nd Ed.), Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989), could be used, although, as will be recognized by those of skill in the art.

20 The nucleic acids to be contacted with the microarray may be prepared in a variety of ways, and may include nucleotides of the subject invention. Such nucleic acids are often labeled fluorescently. Nucleic acid hybridization and wash conditions are chosen so that the population of labeled nucleic acids will specifically hybridize to appropriate, complementary nucleic acids affixed to the matrix. Non-specific binding of the labeled nucleic acids to the array can be decreased by treating the array with a large quantity of
25 non-specific DNA -- a so-called "blocking" step.

When fluorescently labeled probes are used, the fluorescence emissions at each site of a transcript array may be detected by scanning confocal laser microscopy. When two fluorophores are used, a separate scan, using the appropriate excitation line, is carried out for each of the two fluorophores used. Fluorescent microarray scanners are commercially
30 available from Affymetrix, Packard BioChip Technologies, BioRobotics and many other suppliers. Signals are recorded, quantitated and analyzed using a variety of computer software.

According to the method of the invention, the relative abundance of an mRNA in two cells or cell lines is scored as a perturbation and its magnitude determined (i.e., the abundance is different in the two sources of mRNA tested), or as not perturbed (i.e., the relative abundance is the same). As used herein, a difference between the two sources of RNA of at least a factor of about 25% (RNA from one source is 25% more abundant in one source than the other source), more usually about 50%, even more often by a factor of about 2 (twice as abundant), 3 (three times as abundant) or 5 (five times as abundant) is scored as a perturbation. Present detection methods allow reliable detection of difference of an order of about 2-fold to about 5-fold, but more sensitive methods are expected to be developed.

In addition to identifying a perturbation as positive or negative, it is advantageous to determine the magnitude of the perturbation. This can be carried out, as noted above, by calculating the ratio of the emission of the two fluorophores used for differential labeling, or by analogous methods that will be readily apparent to those of skill in the art.

In certain embodiments, the data obtained from such experiments reflects the relative expression of each gene represented in the microarray. Expression levels in different samples and conditions may now be compared using a variety of statistical methods.

12. Pharmaceutical Compositions

Pharmaceutical compositions of this invention include any modulator identified according to the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The term "pharmaceutically acceptable carrier" refers to a carrier(s) that is "acceptable" in the sense of being compatible with the other ingredients of a composition and not deleterious to the recipient thereof.

Methods of making and using such pharmaceutical compositions are also included in the invention. The pharmaceutical compositions of the invention can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra articular, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the modulators described herein are useful for the prevention and treatment of disease and conditions,

including *E. faecalis* mediated diseases and conditions. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w).

5 Alternatively, such preparations contain from about 20% to about 80% active compound.

13. Antimicrobial Agents

The polypeptides of the invention may be used to develop antimicrobial agents for use in a wide variety of applications. The uses are as varied as surface disinfectants, topical
10 pharmaceuticals, personal hygiene applications (e.g., antimicrobial soap, deodorant or the like), additives to cell culture medium, and systemic pharmaceutical products. Antimicrobial agents of the invention may be incorporated into a wide variety of products and used to treat an already existing microbial infection/contamination or may be used prophylactically to suppress future infection/contamination.

15 The antimicrobial agents of the invention may be administered to a site, or potential site, of infection/contamination in either a liquid or solid form. Alternatively, the agent may be applied as a coating to a surface of an object where microbial growth is undesirable using nonspecific absorption or covalent attachment. For example, implants or devices (such as linens, cloth, plastics, heart pacemakers, surgical stents, catheters, gastric tubes,
20 endotracheal tubes, prosthetic devices) can be coated with the antimicrobials to minimize adherence or persistence of bacteria during storage and use. The antimicrobials may also be incorporated into such devices to provide slow release of the agent locally for several weeks during healing. The antimicrobial agents may also be used in association with devices such as ventilators, water reservoirs, air-conditioning units, filters, paints, or other
25 substances. Antimicrobials of the invention may also be given orally or systemically after transplantation, bone replacement, during dental procedures, or during implantation to prevent colonization with bacteria.

In another embodiment, antimicrobial agents of the invention may be used as a food preservative or in treating food products to eliminate potential pathogens. The latter use
30 might be targeted to the fish and poultry industries that have serious problems with enteric pathogens which cause severe human disease. In a further embodiment, the agents of the invention may be used as antimicrobials for food crops, either as agents to reduce post harvest spoilage or to enhance host resistance. The antimicrobials may also be used as

preservatives in processed foods either alone or in combination with antibacterial food additives such as lysozymes.

In another embodiment, the antimicrobials of the invention may be used as an additive to culture medium to prevent or eliminate infection of cultured cells with a
5 pathogen.

EXEMPLIFICATION

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration
10 of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

EXAMPLE 1 Isolation and Cloning of Nucleic Acid

Enterococcus faecalis is a facultative Gram-positive anaerobe bacteria that is associated with both community and hospital acquired infections. Approximately 80% of
15 enterococcal infections in humans are caused by *E. faecalis*. The most common enterococcal-associated nosocomial infections are infections of the urinary tract, followed by surgical wound infections and bacteremia. Other enterococcal infections include intra abdominal and pelvic infections, central nervous system infections, and in rare instances, osteomyelitis and pulmonary infections. The high virulence of the organism and the ability
20 of many strains to resist numerous anti-microbial agents, presents difficult therapeutic issues. Most enterococci are relatively resistant to penicillin, ampicillin, and the ureidopenicillins. *E. faecalis* polynucleotide sequences were obtained from The Institute of Genomic Research (TIGR) (Rockville, MD; www.tigr.org). *E. faecalis* genomic DNA is extracted from a crushed cell pellet (strain V583) and and subjected to 10% sucrose and 2%
25 SDS in a 60°C water bath, followed by the addition of 1 M NaCl for a 40 minute incubation on ice. Impurities, including RNA and proteins, are removed by enzymatic degradation via RNase and phenol-chloroform extractions, respectively. The DNA is then precipitated, washed with ethanol, and quantified by UV absorption.

The coding sequences of the subject nucleic acid sequences (predicted) are obtained
30 by reference to either publicly available databases or from the use of a bioinformatics program that is used to select the coding sequence of interest from the applicable genome. For example, bioinformatics programs that may be used to select the coding sequence of interest from the genome of *E. faecalis* include that described in Nucleic Acids Research,

1999, 27:4636-4641 and the ContigExpress and Translate functionalities of Vector NTI Suite (InforMax).

The coding DNA is amplified from purified genomic DNA using PCR with primers that are identified with a computer program. The PCR primers are selected so as to introduce restriction enzyme cleavage sites at the flanking regions of the DNA (e.g., NdeI and BglII). The forward and reverse primers have SEQ ID NO: 5 and SEQ ID NO: 6. The sequences of the primers are shown in FIGURE 5, and their respective restriction sites and melting temperatures are shown in Table 1 of FIGURE 6.

The PCR reaction is performed using 50-100 ng of chromosomal DNA and 2 Units of a high fidelity DNA Polymerase (for example *Pfu* Turbo (Stratagene) or Platinum *Pfx* (Invitrogen)). The thermocycling conditions for the PCR process include a DNA melting step at 94°C for 45 sec, a primer annealing step at 48°C - 58°C (depending on Primer [T_m]) for 45 sec, and an extension step at 68°C - 72°C (depending on enzyme) for 1 min 45 sec - 2 min 30 sec (depending on size of DNA). After 25-30 cycles, a final blocking step at 72°C for 9 min is carried out.

The amplified nucleic acid product is isolated from the PCR cocktail using silica-gel membrane based column chromatography (Qiagen). The quality of the PCR product is assessed by resolving an aliquot of amplified product on a 1% agarose gel. The DNA is quantified spectrophotometrically at A₂₆₀ or by visualizing the resolved genes with a 302 nm UV-B light source.

The PCR product is directionally cloned into the polylinker region of any of three expression vectors: pET28 (Novagen), pET15 (Novagen) or pGEX (Pharmacia/LKB Biotechnology). Additional restriction enzyme sites may be engineered into the expressions vectors to allow for simultaneous clones to be prepared having different purification tags. After the ligation reaction, the DNA is transformed into competent *E. coli* cells (Strains XL1-Blue (Stratagene) or DH5α (Invitrogen)) via heat shock or electroporation as described in Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989). The expression vectors contain the bacteriophage T7 promoter for RNA polymerase, and the *E. coli* strain used produces T7 RNA polymerase upon induction with isopropyl-β-D-thiogalactoside (IPTG). The sequence of the cloning site adds a Glutathione S-transferase (GST) tag, or a polyhistidine (6X His) tag, at the N- or C- terminus of the recombinant protein. The cloning site also inserts a cleavage site for the thrombin or Tev (Invitrogen)

enzymes between the recombinant protein and the N- or C- terminal GST or polyhistidine tag.

Transformants are selected using the appropriate antibiotic (Ampicillin or Kanamycin) and identified using PCR, or another method, to analyze their DNA. The polynucleotide sequence cloned into the expression construct is then isolated using a modified alkaline lysis method (Birnboim, H.C., and Doly, J. (1979) *Nucl. Acids Res.* 7, 1513-1522.) The sequence of the clone is verified by standard polynucleotide sequencing methods. The published nucleic acid and amino acid sequences are presented in FIGURE 1 and FIGURE 2. The experimentally determined nucleic acid sequence is presented in FIGURE 3, and the amino acid sequence predicted from the sequence of FIGURE 3 is presented in FIGURE 4.

The expression construct is transformed into a bacterial host strain BL21-Gold (DE3) supplemented with a plasmid called pUBS520, which directs expression of tRNA for arginine (agg and aga) and serves to augment the expression of the recombinant protein in the host cell (Gene, vol. 85 (1989) 109-114). The expression construct may also be transformed into BL21-Gold (DE3) without pUBS520, BL21-Gold (DE3) Codon-Plus (RIL) or (RP) (Stratagene) or Roseatta (DE3) (Novagen), the latter two of which contain genes encoding tRNAs. Alternatively, the expression construct may be transformed into BL21 STAR *E. coli* (Invitrogen) cells which has an Rnase deficiency that reduces degradation of recombinant mRNA transcript and therefore increases the protein yield. The recombinant protein is then assayed for positive overexpression in the host and the presence of the protein in the cytoplasmic (water soluble) region of the cell.

EXAMPLE 2 Test Protein Expression and Solubility

(a) Test Expression

Transformed cells are grown in LB medium supplemented with the appropriate antibiotics up to a final concentration of 100 µg/ml. The cultures are shaken at 37°C until they reach an optical density (OD₆₀₀) between 0.6 and 0.7. The cultures are then induced with isopropyl-beta-D-thiogalactopyranoside (IPTG) to a final concentration of 0.5 mM at 15°C for 10 hours, 25°C for 4 hours, or 30°C for 4 hours.

(b) Method One for Determining Protein Solubility Levels

The cells are harvested by centrifugation and subjected to a freeze/thaw cycle. The cells are lysed using detergent, sonication, or incubation with lysozyme. Total and soluble

proteins are assayed using a 26-well BioRad Criterion gel running system. The proteins are stained with an appropriate dye (Coomassie, Silver stain, or Sypro-Red) and visualized with the appropriate visualization system. Typically, recombinant protein is seen as a prominent band in the lanes of the gel representing the soluble fraction.

5 (c) Method Two for Determining Protein Solubility Levels

The soluble and insoluble fractions (in the presence of 6M urea) of the cell pellet are bound to the appropriate affinity column. The purified proteins from both fractions are analysed by SDS-PAGE and the levels of protein in the soluble fraction are determined.

10 The approximate percent solubility of the polypeptide having the sequence of SEQ ID NO: 4 is determined using one of the foregoing methods, and the resulting percent solubility is presented in Table 1 of FIGURE 6.

EXAMPLE 3 Native Protein Expression

15 The expression construct clone encoding the soluble polypeptide having the amino acid sequence of SEQ ID NO: 4 is introduced into an expression host. The resultant cell line is then grown in culture. The method of growth is dependant on whether the protein to be purified is a native protein or a labeled protein. For native and ¹⁵N labeled protein production, a Gold-pUBS520 (as described above), BL21-Gold (DE3) Codon-Plus (RIL) or (RP), or BL21 STAR *E. Coli* cell line is used. For generating proteins metabolically
20 labeled with selenium, the clone is introduced into a strain called B834 (Novagen). The methods for expressing labeled polypeptides of the invention are described in the Examples that follow.

In one method for expressing an unlabeled polypeptide of the invention, 2L LB cultures or 1L TB cultures are inoculated with a 1% (v/v) starter culture (OD₆₀₀ of 0.8).
25 The cultures are shaken at 37°C and 200 rpm and grown to an OD₆₀₀ of 0.6-0.8 followed by induction with 0.5mM IPTG at 15°C and 200 rpm for at least 10 hours or at 25°C for 4 hours.

The cells are harvested by centrifugation and the pellets are resuspended in 25 ml HEPES buffer (50 mM, pH 7.5), supplemented with 100µl of protease inhibitors (PMSF
30 and benzamidine (Sigma)) and flash-frozen in liquid nitrogen.

Alternatively, for an unlabeled polypeptide of the invention, a starter culture is prepared in a 300 mL Tunair flask (Shelton Scientific) by adding 20 mL of medium having

47.6 g/L of Terrific Broth and 1.5% glycerol in dH₂O followed by autoclaving for 30 minutes at 121°C and 15 psi. When the broth cools to room temperature, the medium is supplemented with 6.3 μ M CoCl₂·6H₂O, 33.2 μ M MnSO₄·5H₂O, 5.9 μ M CuCl₂·2H₂O, 8.1 μ M H₃BO₃, 8.3 μ M Na₂MoO₄·2H₂O, 7 μ M ZnSO₄·7H₂O, 108 μ M FeSO₄·7H₂O, 68 μ M CaCl₂·2H₂O, 4.1 μ M AlCl₃·6H₂O, 8.4 μ M NiCl₂·6H₂O, 1 mM MgSO₄, 0.5% v/v of Kao and Michayluk vitamins mix (Sigma; Cat. No. K3129), 25 μ g/mL Carbenicillin, and 50 μ g/mL Kanamycin. The medium is then inoculated with several colonies of the freshly transformed expression construct of interest. The culture is incubated at 37°C and 260 rpm for about 3 hours and then transferred to a 2.5L Tunair Flask containing 1L of the above media. The 1L culture is then incubated at 37°C with shaking at 230-250 rpm on an orbital shaker having a 1 inch orbital diameter. When the culture reaches an OD₆₀₀ of 3-6 it is induced with 0.5 mM IPTG. The induced culture is then incubated at 15°C with shaking at 230-250 rpm or faster for about 6-15 hours. The cells are harvested by centrifugation at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL ice cold binding buffer (Hepes 50 mM, pH 7.5) and 100 μ L of protease inhibitors (50 mM PMSF and 100 mM Benzamidine, stock concentration) and flash frozen.

EXAMPLE 4 Expression of Selmet Labeled Polypeptides

The freshly transformed cell, harboring a plasmid with a nucleic acid encoding a polypeptide of the invention, is inoculated into 20 ml of NMM (New Minimal Medium) and shaken at 37°C for 8-9 hours. This culture is then transferred into a 6L Erlenmeyer flask containing 2L of minimum medium (M9). The media is supplemented with all amino acids except methionine. All amino acids are added as a solution except for Tyrosine, Tryptophan and Phenylalanine which are added to the media in powder format. As well the media is supplemented with MgSO₄ (2mM final concentration), FeSO₄·7H₂O (25mg/L final concentration), Glucose (0.4% final concentration), CaCl₂ (0.1mM final concentration) and Seleno-L-Methionine (40mg/L final concentration). When the OD₆₀₀ of the cell culture reaches 0.8-0.9, IPTG (0.4 mM final concentration) is added to the medium for protein induction, and the cell culture is kept shaking at 15°C for 10 hours. The cells are harvested by centrifugation at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 μ L of protease inhibitors (PMSF and Benzamidine) and flash frozen.

Alternatively, a starter culture is prepared in a 300 mL Tunair flask (Shelton Scientific) by adding 50 mL of sterile medium having 10% 10XM9 (37.4 mM NH_4Cl (Sigma; Cat. No. A4514), 44 mM KH_2PO_4 (Bioshop, Ontario, Canada; Cat. No. PPM 302), 96 mM Na_2HPO_4 (Sigma; Cat. No. S2429256), and 96 mM $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ (Sigma; Cat. No. S9390) final concentration), 450 μM alanine, 190 μM arginine, 302 μM asparagine, 300 μM aspartic acid, 330 μM cysteine, 272 μM glutamic acid, 274 μM glutamine, 533 μM glycine, 191 μM histidine, 305 μM isoleucine, 305 μM leucine, 220 μM lysine, 242 μM phenylalanine, 348 μM proline, 380 μM serine, 336 μM threonine, 196 μM tryptophan, 220 μM tyrosine, and 342 μM valine, 204 μM Seleno-L-Methionine (Sigma; Cat. No. S3132), 0.5% v/v of Kao and Michayluk vitamins mix (Sigma; Cat. No. K3129), 2 mM MgSO_4 (Sigma; Cat. No. M7774), 90 μM $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (Sigma; Cat. No. F8633), 0.4% glucose (Sigma; Cat. No. G-5400), 100 μM CaCl_2 (Bioshop, Ontario, Canada; Cat. No. CCL 302), 50 $\mu\text{g/mL}$ Ampicillin, and 50 $\mu\text{g/mL}$ Kanamycin in dH_2O . The medium is then inoculated with several colonies of *E. coli* B834 cells (Novagen) freshly transformed with an expression construct clone encoding the polypeptide of interest. The culture is then incubated at 37°C and 200 rpm until it reaches an OD_{600} of ~1 and is then transferred to a 2.5L Tunair Flask containing 1L of the above media. The 1L culture is incubated at 37°C with shaking at 200 rpm until the culture reaches an OD_{600} of 0.6-0.8 and is then induced with 0.5 mM IPTG. The induced culture is incubated overnight at 15°C with shaking at 200 rpm. The cells are harvested by centrifugation at 4200 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 15 mL ice cold binding buffer (Hepes 50 mM, pH 7.5) and 100 μL of protease inhibitors (50 mM PMSF and 100 mM Benzamidine, stock concentration) and flash frozen.

Alternatively, the cell harboring a plasmid with a nucleic acid encoding a polypeptide of the invention is inoculated into 10 ml of M9 minimum medium and kept shaking at 37°C for 8-9 hours. This culture is then transferred into a 2L Baffled Flask (Corning) containing 1L minimum medium. The media is supplemented with all amino acids except methionine. All are added as a solution, except for Phenylalanine, Alanine, Valine, Leucine, Isoleucine, Proline, and Tryptophan which are added to the media in powder format. As well the media is supplemented with MgSO_4 (2mM final concentration), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (25 mg/L final concentration), Glucose (0.5% final concentration), CaCl_2 (0.1 mM final concentration) and Seleno-Methionine (50 mg/L final concentration). When the

OD₆₀₀ of the cell culture reaches 0.8-0.9, IPTG (0.8 mM final concentration) is added to the medium for protein induction, and the cell culture is kept shaking at 25°C for 4 hours. The cells are harvested by centrifuged at 3500 rpm at 4°C for 20 minutes and the cell pellet is resuspended in 10 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitors (PMSF and Benzamidine) and flash frozen.

EXAMPLE 5 Expression of ¹⁵N Labeled Polypeptides

The cell, harboring a plasmid with a nucleic acid encoding a polypeptide of the invention, is inoculated into 2L of minimal media (containing ¹⁵N isotope, Cambridge Isotope Lab) in a 6L Erlenmeyer flask. The minimal media is supplemented with 0.01 mM ZnSO₄, 0.1 mM CaCl₂, 1 mM MgSO₄, 5 mg/L Thiamine.HCl, and 0.4% glucose. The 2L culture is grown at 37°C and 200 rpm to an OD₆₀₀ of between 0.7-0.8. The culture is then induced with 0.5 mM IPTG and allowed to shake at 15°C for 14 hours. The cells are harvested by centrifugation and the cell pellet is resuspended in 15 mL cold binding buffer and 100µl of protease inhibitor and flash frozen. The protein is then purified as described below.

Alternatively, the freshly transformed cell, harboring a plasmid with the gene of interest, is inoculated into 10 mL of M9 media (with ¹⁵N isotope) and supplemented with 0.01 mM ZnSO₄, 0.1 mM CaCl₂, 1 mM MgSO₄, 5 mg/L Thiamine.HCl, and 0.4% glucose. After 8-10 hours of growth at 37°C, the culture is transferred to a 2L Baffled flask (Corning) containing 990 mL of the same media. When OD₆₀₀ of the culture is between 0.7-0.8, protein production is initiated by adding IPTG to a final concentration of 0.8 mM and lowering the temperature to 25°C. After 4 hours of incubation at this temperature, the cells are harvested, and the cell pellet is resuspended in 10 mL cold binding buffer (Hepes 50 mM, pH 7.5) and 100 µl of protease inhibitor and flash frozen.

EXAMPLE 6 Method One for Purifying Polypeptides of the Invention

The frozen pellets are thawed and sonicated to lyse the cells (5 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR). The lysates are clarified by centrifugation at 14,000 rpm for 60 min at 4°C to remove insoluble cellular debris. The supernatants are removed and supplemented with 1 µl of Benzonase Nuclease (25 U/µl, Novagen).

The recombinant protein is purified using DE52 (anion exchanger, Whatman) and Ni-NTA columns (Qiagen). The DE52 columns (30 mm wide, Biorad) are prepared by mixing 10 grams of DE52 resin in 25 ml of 2.5 M NaCl per protein sample, applying the resin to the column and equilibrating with 30 ml of binding buffer (50 mM in HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 5 mM imidazole). Ni-NTA columns are prepared by adding 3.5-8 ml of resin to the column (20 mm wide, Biorad) based on the level of expression of the recombinant protein and equilibrating the column with 30 ml of binding buffer. The columns are arranged in tandem so that the protein sample is first passed over the DE52 column and then loaded directly onto the Ni-NTA column.

The Ni-NTA columns are washed with at least 150 ml of wash buffer (50mM HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 30 mM imidazole) per column. A pump may be used to load and/or wash the columns. The protein is eluted off of the Ni-NTA column using elution buffer (50 mM in HEPES, pH 7.5, 5% glycerol (v/v), 0.5 M NaCl, 250 mM imidazole) until no more protein is observed in the aliquots of eluate as measured using Bradford reagent (Biorad). The eluate is supplemented with 1 mM of EDTA and 0.2 mM DTT.

The samples are assayed by SDS-PAGE and stained with Coomassie Blue, with protein purity determined by visual staining.

Two methods may be used to remove the His tag located at either the C or N-terminus. In certain instances, the His tag may not be removed. In either case, the expressed polypeptide will have additional residues attributable to the His tag, as shown in the following table:

<i>SEQ ID NO for Additional Residues</i>	<i>Additional Residues</i>	<i>Type of Tag and Whether or Not Removed</i>
N/A	GSH	His tag removed from N-terminus
SEQ ID NO: 7	MGSSHHHHHHSSGLVPRG SH	His tag not removed from N-terminus
SEQ ID NO: 8	GSENLVFQGHHHHHH	His tag removed from C-terminus
SEQ ID NO: 9	GSENLVFQ	His tag not removed from C-terminus

In method one, a sample of purified polypeptide is supplemented with 2.5 mM CaCl_2 and an appropriate amount of thrombin (the amount added will vary depending on the activity of the enzyme preparation) and incubated for ~20-30 minutes on ice in order to

remove the His tag. In method two, a sample of purified polypeptide is combined with thirty units of recombinant TEV protease in 50 mmol TRIS HCl pH = 8.0, 0.5 mmol EDTA and 1 mmol DTT, followed by incubation at 4°C overnight, to remove the His tag.

5 The protein sample is then dialyzed in dialysis buffer (10mM HEPES, pH 7.5, 5% glycerol (v/v) and 0.5 M NaCl) for at least 8 hours using a Slide-A-Lyzer (Pierce) appropriate for the molecular weight of the recombinant protein. An aliquot of the cleaved and dialyzed samples is then assayed by SDS-PAGE and stained with Coomassie Blue to determine the purity of the protein and the success of cleavage.

10 The remainder of the sample is centrifuged at 2700 rpm at 4°C for 10-15 minutes to remove any precipitant and supplemented with 100 µl of protease inhibitor cocktail (0.1 M benzamidine and 0.05 M PMSF) (NO Bioshop). The protein is then applied to a second Ni-NTA column (~8 ml of resin) to remove the His-tags and eluted with binding buffer or wash buffer until no more protein is eluting off the column as assayed using the Bradford reagent. The eluted sample is supplemented with 1 mM EDTA and 0.6 mM of DTT and
15 concentrated to a final volume of ~15 mls using a Millipore Concentrator with an appropriately sized filter at 2700 rpm at 4°C. The samples are then dialyzed overnight against crystallization buffer and concentrated to final volume of 0.3-0.7 ml.

EXAMPLE 7 Method Two for Purifying Polypeptides of the Invention

20 The frozen pellets are thawed and supplemented with 100 µl of protease inhibitor (0.1 M benzamidine and 0.05 M PMSF), 0.5% CHAPS, and 4 U/ml Benzonase Nuclease. The sample is then gently rocked on a Nutator (VWR, setting 3) at room temperature for 30 minutes. The cells are then lysed by sonication (1 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR) and an aliquot is saved for a gel sample.

25 The recombinant protein is purified using a three column system. The columns are set up in tandem so that the lysate flows from a Biorad Econo (5.0 x 30 cm x 589 ml) "lysate" column onto a Biorad Econo (2.5 x 20 cm x 98 ml) DE52 column and finally onto a Biorad Econo (1.5 x 15 cm x 27 ml) Ni-NTA column. The lysate is mixed with 10 g of equilibrated DE52 resin and diluted to a total volume of 300 ml with binding buffer. This
30 mixture is poured into the first column which is empty. The remainder of the purification procedure is described in EXAMPLE 6 above.

EXAMPLE 8 Method Three for Purifying Polypeptides of the Invention

The frozen pellets are thawed and sonicated to lyse the cells (5 x 30 seconds, output 4 to 5, 80% duty cycle, in a Branson Sonifier, VWR). The lysates are clarified by centrifugation at 14000 rpm for 60 min at 4°C to remove insoluble cellular debris. The
5 supernatants are removed and supplemented with 1 µl of Benzonase Nuclease (25 U/µl, Novagen).

The recombinant protein is purified using DE52 (anion exchanger, Whatman) and Glutathione sepharose columns (Glutathione-Superflow resin, Clontech). The DE52 columns (30 mm wide, Biorad) are prepared by mixing 10 grams of DE52 resin in 20 ml of
10 2.5 M NaCl per protein sample, applying the resin to the column and equilibrating with 30 ml of loading buffer (50mM in HEPES, pH 7.5, 10% glycerol (v/v), 0.5 M NaCl, 1 mM EDTA, 1 mM DTT). Glutathione sepharose columns are prepared by adding 3 ml of resin to the column (20 mm wide, Biorad) and equilibrating the column with 30 ml of loading buffer. The columns are arranged in tandem so that the protein sample is first passed over
15 the DE52 column and then loads directly onto the Glutathione sepharose column.

The columns are washed with at least 150 ml of loading buffer supplemented with protease inhibitor cocktail (0.1 M benzamidine and 0.05 M PMSF) per column. A pump may be used to load and/or wash the columns. The protein is eluted off of the Glutathione sepharose column using elution buffer (20mM HEPES, pH 7.5, 0.5 M NaCl, 1 mM EDTA,
20 1 mM DTT; 25 mM glutathione (reduced form)) until no more protein is observed in the aliquots of eluate as measured using Biorad Bradford reagent.

The GST tag may be removed using thrombin or other procedures known in the art. The protein samples are then dialyzed into crystallization buffer (10 mM Hepes, pH 7.5,
25 500 mM NaCl) to remove free glutathione and assayed by SDS-PAGE followed by staining with Coomassie blue. Prior to use or storage, the samples are concentrated to final volume of 0.3-0.5 ml.

Using one or more of the methods described above, purified polypeptide having SEQ ID NO: 4 is obtained in a yield of approximately 31.03 mg per liter of culture. The purified polypeptide is essentially the only protein visualized in the SDS-PAGE assay using
30 Coomassie Blue described above, which is at least about 95% or greater purity. The polypeptide so expressed and purified is His tagged (having sequence GSENLVYFQGHHHHHH) at the C-terminus as described above.

The protein samples so prepared and purified may be used in the biophysical studies that follow, with or without the His tag or the residual amino acids resulting from removal of the His tag. In certain instances, such as EXAMPLE 11, the polypeptide used may be a fusion protein with a specific tag.

5 A stable solution of purified polypeptide having SEQ ID NO: 4, prepared and purified as described above, may be prepared with 21.40 mg (or a lesser amount) of protein in one ml of either the dialysis or crystallization buffers (or possibly both) described above in EXAMPLE 7 or EXAMPLE 9, respectively.

\Certain of the foregoing information is also set forth in Table 1 of FIGURE 6

10 For certain polypeptides of the invention, truncated polypeptides are prepared. Truncated polypeptides are generated via a "shot gun" approach whereby 1 to about 15 or more residues may be deleted from the N and/or C termini of the polypeptide of interest in a sequential pattern, in a variety of combinations of deletions. Alternatively, truncated polypeptides may be prepared by rational design, using multiple sequence alignments of the
15 protein and other orthologues, secondary structure prediction and tertiary structure of a related protein (if available) as guiding tools. In such cases, from 1 to about 20 amino acids or more may be deleted from the N and/or C termini. Truncated constructs are PCR amplified from genomic DNA and cloned into expression vectors as described above for the various pathogens. Truncation constructs are then tested for expression and solubility
20 as described above. The most highly expressed and soluble truncated polypeptides may be subject to further purification and characterization as provided herein.

EXAMPLE 9 Mass Spectrometry Analysis via Fingerprint Mapping

A gel slice from a purification protocol described above containing a polypeptide of
25 the invention is cut into 1 mm cubes and 10 to 20 μ l of 1% acetic acid is added. After washing with 100 - 150 μ l HPLC grade water and removal of the liquid, acetonitrile (~200 μ l, approximately 3 to 4 times the volume of the gel particles) is added followed by incubation at room temperature for 10 to 15 minutes with vortexing. A second acetonitrile wash may be required to completely dehydrate the gel particles. The protein in the gel
30 particles is reduced at 50 degrees Celsius using 10 mM dithiothreitol (in 100 mM ammonium bicarbonate) and then alkylated at room temperature in the dark using 55 mM iodoacetamide (in 100 mM ammonium bicarbonate). The gel particles are rinsed with a

minimal volume of 100 mM ammonium bicarbonate before a trypsin (50 mM ammonium bicarbonate, 5 mM CaCl₂, and 12.5 ng/μl trypsin) solution is added. The gel particles are left on ice for 30 to 45 minutes (after 20 minutes incubation more trypsin solution is added). The excess trypsin solution is removed and 10 to 15 μl digestion buffer without trypsin is added to ensure the gel particles remain hydrated during digestion. After digestion at 37°C, the supernatant is removed from the gel particles. The peptides are extracted from the gel particles with 2 changes of 100 μL of 100 mM ammonium bicarbonate with shaking for 45 minutes and pooled with the initial gel supernatant. The extracts are acidified to 1% (v/v) with 100% acetic acid.

10 The tryptic peptides are purified with a C18 reverse phase resin. 250 μL of dry resin is washed twice with methanol and twice with 75% acetonitrile/1% acetic acid. A 5:1 slurry of solvent:resin is prepared with 75% acetonitrile/1% acetic acid. To the extracted peptides, 2 μL of the resin slurry is added and the solution is shaken for 30 minutes at room temperature. The supernatant is removed and replaced with 200 μL of 2% acetonitrile/1% acetic acid and shaken for 5-15 minutes. The supernatant is removed and the peptides are eluted from the resin with 15 μL of 75% acetonitrile/1% acetic acid with shaking for about 5 minutes. The peptide and slurry mixture is applied to a filter plate and centrifuged, and the filtrate is collected and stored at -70°C until use.

Alternatively, the tryptic peptides are purified using ZipTip_{C18} (Millipore, Cat # ZTC18S960). The ZipTips are first pre-wetted by aspirating and dispensing 100% methanol. The tips are then washed with 2% acetonitrile/1% acetic acid (5 times), followed by 65% acetonitrile/1% acetic acid (5 times) and returned to 2% acetonitrile/1% acetic acid (10 times). The digested peptides are bound to the ZipTips by aspirating and dispensing the samples 5 times. Salts are removed by washing ZipTips with 2% acetonitrile/1% acetic acid (5 times). 10 μL of 65% acetonitrile/1% acetic acid is collected by the ZipTips and dispensed into a 96-well microtitre plate.

Analytical samples containing tryptic peptides are subjected to MALDI-TOF mass spectrometry. Samples are mixed 1:1 with a matrix of α-cyano-4-hydroxy-*trans*-cinnamic acid. The sample/matrix mixture is spotted on to the MALDI sample plate with a robot, either a Gilson 215 liquid handler or BioMek FX laboratory automation workstation (Beckman). The sample/matrix mixture is allowed to dry on the plate and is then introduced into the mass spectrometer. Analysis of the peptides in the mass spectrometer is

conducted using both delayed extraction mode (400 ns delay) and an ion reflector to ensure high resolution of the peptides.

Internally-calibrated tryptic peptide masses are searched against databases using a correlative mass matching algorithm. The Proteometrics software package (ProteoMetrics) is utilized for batch database searching of tryptic peptide mass spectra. Statistical analysis is performed on each protein match to determine its validity. Typical search constraints include error tolerances within 0.1 Da for monoisotopic peptide masses, carboxyamidomethylation of cysteines, no oxidation of methionines allowed, and 0 or 1 missed enzyme cleavages. The software calculates the probability that a candidate in the database search is the protein being analyzed, which is expressed as the Z-score. The Z-score is the distance to the population mean in unit of standard deviation and corresponds to the percentile of the search in the random match population. If a search is in the 95th percentile, for example, about 5% of random matches could yield a higher Z-score than the search. A Z-score of 1.282 for a search indicates that the search is in the 90th percentile, a Z-score of 1.645 indicates that the search is in the 95th percentile, a Z-score of 2.326 indicates that the search is in the 99th percentile, and a Z-score of 3.090 indicates that the search is in the 99.9th percentile.

As shown in FIGURE 8, and listed in Table 1 of FIGURE 6, are the results of the mass search described above. The Z-score for the polypeptide of the present invention is 2.41. The number of matched peptides for the polypeptide of the present invention is 14. The minimum sequence coverage for the polypeptide of the present invention is 31%. From this experiment, the identity of the subject polypeptide has been confirmed.

EXAMPLE 10 Mass Spectrometry Analysis via High Mass

A matrix solution of 25 mg/mL of 3,5-dimethoxy-4-hydroxycinnamic acid (sinapinic acid) in 66% (v/v) acetonitrile/1% (v/v) acetic acid is prepared along with an internal calibrant of carbonic anhydrase. On to a stainless steel polished MALDI target, 1.5 μ L of a protein solution (concentration of 2 μ g/ μ L) is spotted, followed immediately by 1.5 μ L of matrix. 3 μ L of 40% (v/v) acetonitrile/1% (v/v) acetic acid is then added to each spot has dried. The sample is either spotted manually or utilizing a Gilson 215 liquid handler or BioMek FX laboratory automation workstation (Beckman). The MALDI-TOF instrument utilizes positive ion and linear detection modes. Spectra are acquired automatically over a

mass to charge range from 0-150,000 Da, pulsed ion extraction delay is set at 200 ns, and 600 summed shots of 50-shot steps are completed.

The theoretical molecular weight of the protein for MALDI-TOF is determined from its amino acid sequence, taking into account any purification tag or residue thereof still present and any labels (e.g., selenomethionine or ^{15}N). To account for ^{15}N incorporation, an amount equal to the theoretical molecular weight of the protein divided by 70 is added. The mass of water is subtracted from the overall molecular weight. The MALDI-TOF spectrum is calibrated with the internal calibrant of carbonic anhydrase (observed as either $[\text{MH}^+_{\text{avg}}]$ 29025 or $[\text{MH}_2^{2+}]$ 14513).

FIGURE 9 displays a MALDI-TOF-generated mass spectrum of the intact polypeptide of the present invention. The experimentally determined molecular weight of the polypeptide is listed in Table 1 of FIGURE 6. In certain instances, a lower mass to charge peak may also be present, which signifies the presence of doubly-charged molecular ion peak $[\text{MH}_2^{2+}]$ of the protein.

EXAMPLE 11 Method One for Isolating and Identifying Interacting Proteins

(a) Method One for Preparation of Affinity Column

Micro-columns are prepared using forceps to bend the ends of P200 pipette tips and adding 10 μl of glass beads to act as a column frit. Six micro-columns are required for every polypeptide to be studied. The micro-columns are placed in a 96-well plate that has 1 mL wells. Next, a series of solutions of the polypeptide having SEQ ID NO: 4 or other polypeptide of the invention, prepared and purified as described above and with a GST tag on either terminus, is prepared so as to give final amounts of 0, 0.1, 0.5, 1.0, and 2.0 mg of ligand per ml of resin volume.

A slurry of Glutathione-Sepharose 4B (Amersham) is prepared and 0.5 ml slurry/ligand is removed (enough for six 40- μg aliquots of resin). Using a glass frit Buchner funnel, the resin is washed sequentially with three 10 ml portions each of distilled H_2O and 1 M ACB (20 mM HEPES pH 7.9, 1 M NaCl, 10% glycerol, 1 mM DTT, and 1 mM EDTA). The Glutathione-Sepharose 4B is completely drained of buffer, but not dried. The Glutathione-Sepharose 4B is resuspended as a 50% slurry in 1 M ACB and 80 μl is added to each micro-column to obtain 40 μg /column. The buffer containing the ligand concentration series is added to the columns and allowed to flow by gravity. The resin and

ligand are allowed to cross-link overnight at 4°C. In the morning, micro-columns are washed with 100 µl of 1 M ACB and allowed to flow by gravity. This is repeated twice more and the elutions are tested for cross-linking efficiency by measuring the amount of unbound ligand. After washing, the micro-columns are equilibrated using 200 µl of 0.1 M
5 ACB (20 mM HEPES pH 7.5, 0.1 M NaCl, 10% glycerol, 1 mM DTT, 1 mM EDTA).

In another method, the recombinant GST fusion protein can be replaced by a hexahistidine fusion peptide for use with NTA-Agarose (Qiagen) as the solid support. No adaptation to the above protocol is required for the substitution of NTA agarose for GST Sepharose except that the recombinant protein requires a six histidine fusion peptide in
10 place of the GST fusion.

(b) Method Two for Preparation of Affinity Column

In an alternative method, GST-Sepharose 4B may be replaced by Affi-gel 10 Gel (Bio-Rad). The column resin for affinity chromatography could also be Affigel 10 resin which allows for covalent attachment of the protein ligand to the micro affinity column. An
15 adaptation to the above protocol for the use of this resin is a pre-wash of the resin with 100% isopropanol. No fusion peptides or proteins are required for the use of Affigel 10 resin.

(c) Method One for Bacterial Extract Preparation

An *E. faecalis* extract is prepared from cell pellets using a French press followed by
20 sonication. An *E. faecalis* cell pellet (~6 g) is suspended in 3 pellet volumes (~20 ml final volume) of 20 mM HEPES pH 7.5, 150 mM NaCl, 10% glycerol, 10 mM MgSO₄, 10 mM CaCl₂, 1 mM DTT, 1 mM PMSF, 1 mM benzamidine, 40 µg/ml RNase A, 75 units/ml S1 nuclease, and 40 units/ml DNase 1. The cell suspension is lysed with one pass with a French Pressure Cell followed by sonication on ice using three bursts of 20 seconds each.
25 The lysate is agitated at 4°C for 30 minutes, brought up to 0.5 M NaCl and then incubated for an additional 30 min at 4°C with agitation. The lysate is centrifuged at 20,000 rpm for 1 hr in a JA25.50 Beckman rotor. The supernatant is removed and dialyzed overnight in a 3,500 Mr dialysis membrane against dialysis buffer (20 mM HEPES pH 7.5, 10 % glycerol, 1 mM DTT, 1 mM EDTA, 100 mM NaCl, 10 mM MgSO₄, 10 mM CaCl₂, 1 mM
30 benzamidine, and 1 mM PMSF). The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at -70°C.

(d) Method Two for Bacterial Extract Preparation

Bacterial cell extracts from *E. faecalis* are prepared from cell pellets using a Bead-Beater apparatus (Bio-spec Products Inc.) and zirconia beads (0.1 mm diameter). The bacterial cell pellet is suspended (~6 g) is suspended in 3 pellet volumes (~20 ml final volume) of 20 mM HEPES pH 7.5, 150 mM NaCl, 10% glycerol, 10 mM MgSO₄, 10 mM CaCl₂, 1 mM DTT, 1 mM PMSF, 1 mM benzamidine, 40 µg/ml RNase A, 75 units/ml S1 nuclease, and 40 units/ml DNase 1. The cells are lysed with 10 pulses of 30 sec between 90 sec pauses at a temperature of -5 °C. The lysate is separated from the zirconia beads using a standard column apparatus. The lysate is centrifuged at 20000 rpm (48000 x g) in a Beckman JA25.50 rotor. The supernatant is removed and dialyzed overnight at 4 °C against dialysis buffer (20 mM HEPES pH 7.5, 10 % glycerol, 1 mM DTT, 1 mM EDTA, 100 mM NaCl, 10 mM MgSO₄, 10 mM CaCl₂, 1 mM benzamidine, and 1 mM PMSF). The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at -70°C.

(e) HeLa Cell Extract Preparation

A HeLa cell extract is prepared in the presence of protease inhibitors. Approximately 30 g of Hela cells are submitted to a freeze/thaw cycle and then divided into two tubes. To each tube 20 ml of Buffer A (10 mM HEPES pH 7.9, 1.5 mM MgCl, 10 mM KCl, 0.5 mM DTT, 0.5 mM PMSF) and a protease inhibitor cocktail are added. The cell suspension is homogenized with 10 strokes (2 x 5 strokes) to lyse the cells. Buffer B (15 ml per tube) is added (50 mM HEPES pH 7.9, 1.5 mM MgCl, 1.26 M NaCl, 0.5 mM DTT, 0.5 mM PMSF, 0.5 mM EDTA, 75% glycerol) to each tube followed by a second round of homogenization (2 x 5 strokes). The lysates are stirred on ice for 30 minutes followed by centrifugation 37,000 rpm for 3 hr at 4°C in a Ti70 fixed angle Beckman rotor. The supernatant is removed and dialyzed overnight in a 10,000 Mr dialysis membrane against dialysis buffer (20 mM HEPES pH 7.9, 10% glycerol, 1 mM DTT, 1 mM EDTA, and 1 M NaCl). The dialyzed protein extract is removed from the dialysis tubing and frozen in one ml aliquots at -70°C.

(f) Affinity Chromatography

Cell extract is thawed and diluted to 5 mg/ml prior to loading 5 column volumes onto each micro-column. Each column is washed with 5 column volumes of 0.1 M ACB. This washing is repeated once. Each column is then washed with 5 column volumes of 0.1 M ACB containing 0.1% Triton X-100. The columns are eluted with 4 column volumes of 1% sodium dodecyl sulfate into a 96 well PCR plate. To each eluted fraction is added one-tenth volume of 10-fold concentrated loading buffer for SDS-PAGE.

(g) Resolution of the Eluted Proteins and Detection of Bound Proteins

The components of the eluted samples are resolved on SDS-polyacrylamide gels containing 13.8% polyacrylamide using the Laemmli buffer system and stained with silver nitrate. The bands containing the interacting protein are excised with a clean scalpel. The gel volume is kept to a minimum by cutting as close to the band as possible. The gel slice is placed into one well of a low protein binding, 96-well round-bottom plate. To the gel slices is added 20 µl of 1% acetic acid.

EXAMPLE 12 Method Two for Isolating and Identifying Interacting Proteins

Interacting proteins may be isolated using immunoprecipitation. Naturally-occurring bacterial or eukaryotic cells are grown in defined growth conditions or the cells can be genetically manipulated with a protein expression vector. The protein expression vector is used to transiently transfect the cDNA of interest into eukaryotic or prokaryotic cells and the protein is expressed for up to 24 or 48 hours. The cells are harvested and washed three times in sterile 20 mM HEPES (pH7.4)/Hanks balanced salts solution (H/H). The cells are finally resuspended in culture media and incubated at 37°C for 4-8 hr.

The harvested cells may be subjected to one or more culture conditions that may alter the protein profile of the cells for a given period of time. The cells are collected and washed with ice-cold H/H that includes 10 mM sodium pyrophosphate, 10 mM sodium fluoride, 10 mM EDTA, and 1 mM sodium orthovanadate. The cells are then lysed in lysis buffer (50 mM Tris-HCl (pH 8.0), 150 mM NaCl, 1% Triton X-100, 10 mM sodium pyrophosphate, 10mM sodium fluoride, 10 mM EDTA, 1 mM sodium orthovanadate, 1 µg/mL PMSF, 1 µg/mL aprotinin, 1 µg/mL leupeptin, and 1 µg/mL pepstatin A) by gentle mixing, and placed on ice for 5 minutes. After lysis, the lysate is transferred to centrifuge tubes and centrifuged in an ultracentrifuge at 75000 rpm for 15 min at 4°C. The supernatant is transferred to eppendorf tubes and pre-cleared with 10 µl of rabbit pre-immune antibody on a rotator at 4°C for 1 hr. Forty µl of protein A-Sepharose (Amersham) is then added and incubated at 4°C overnight on a rotator.

The protein A-Sepharose beads are harvested and the supernatant removed to a fresh eppendorf tube. Immune antibody is added to supernatant and rotated for 1 hr at 4°C. Thirty µl of protein A-Sepharose is then added and the mixture is further rotated at 4°C for 1 hr. The beads are harvested and the supernatant is aspirated. The beads are washed three

times with 50 mM Tris (pH 8.0), 150 mM NaCl, 0.1% Triton X-100, 10 mM sodium fluoride, 10 mM sodium pyrophosphate, 10 mM sodium orthovanadate, and 10 mM EDTA. Dry the beads with a 50 µl Hamilton syringe. Laemmli loading buffer containing 100 mM DTT is added to the beads and samples are boiled for 5 min. The beads are spun down and
5 the supernatant is loaded onto SDS-PAGE gels. Comparison of the control and experimental samples allows for the selection of polypeptides that interact with the protein of interest.

EXAMPLE 13 Sample for Mass Spectrometry of Interacting Proteins

10 The gel slices are cut into 1 mm cubes and 10 to 20 µl of 1% acetic acid is added. The gel particles are washed with 100 - 150 µl of HPLC grade water (5 minutes with occasional mixing), briefly centrifuged, and the liquid is removed. Acetonitrile (~200 µl, approximately 3 to 4 times the volume of the gel particles) is added followed by incubation at room temperature for 10 to 15 minutes with vortexing. A second acetonitrile wash may
15 be required to completely dehydrate the gel particles. The sample is briefly centrifuged and all the liquid is removed.

The protein in the gel particles is reduced at 50 degrees Celsius using 10 mM dithiothreitol (in 100 mM ammonium bicarbonate) for 30 minutes and then alkylated at room temperature in the dark using 55 mM iodoacetamide (in 100 mM ammonium
20 bicarbonate). The gel particles are rinsed with a minimal volume of 100 mM ammonium bicarbonate before a trypsin (50 mM ammonium bicarbonate, 5 mM CaCl₂, and 12.5 ng/µl trypsin) solution is added. The gel particles are left on ice for 30 to 45 minutes (after 20 minutes incubation more trypsin solution is added). The excess trypsin solution is removed and 10 to 15 µl digestion buffer without trypsin is added to ensure the gel particles remain
25 hydrated during digestion. The samples are digested overnight at 37°C.

The following day, the supernatant is removed from the gel particles. The peptides are extracted from the gel particles with 2 changes of 100 µL of 100 mM ammonium bicarbonate with shaking for 45 minutes and pooled with the initial gel supernatant. The extracts are acidified to 1% (v/v) with 100% acetic acid.

30 (a) Method One for Purification of Tryptic Peptides

The tryptic peptides are purified with a C18 reverse phase resin. 250 µL of dry resin is washed twice with methanol and twice with 75% acetonitrile/1% acetic acid. A 5:1

slurry of solvent : resin is prepared with 75% acetonitrile/1% acetic acid. To the extracted peptides, 2 μ L of the resin slurry is added and the solution is shaken at moderate speed for 30 minutes at room temperature. The supernatant is removed and replaced with 200 μ L of 2% acetonitrile/1% acetic acid and shaken for 5-15 minutes with moderate speed. The
5 supernatant is removed and the peptides are eluted from the resin with 15 μ L of 75% acetonitrile/1% acetic acid with shaking for about 5 minutes. The peptide and slurry mixture is applied to a filter plate and centrifuged for 1-2 minutes at 1000 rpm, the filtrate is collected and stored at -70°C until use.

(b) Method Two for Purification of Tryptic Peptides

10 Alternatively, the tryptic peptides may be purified using ZipTip_{C18} (Millipore, Cat # ZTC18S960). The ZipTips are first pre-wetted by aspirating and dispensing 100% methanol 5 times. The tips are then washed with 2% acetonitrile/1% acetic acid (5 times), followed by 65% acetonitrile/1% acetic (5 times) and returned to 2% acetonitrile/1% acetic acid (5 times). The ZipTips are replaced in their rack and the residual solvent is eliminated.
15 The ZipTips are washed again with 2% acetonitrile/1% acetic acid (5 times). The digested peptides are bound to the ZipTips by aspirating and dispensing the samples 5 times. Salts are removed by washing ZipTips with 2% acetonitrile/1% acetic acid (5 times). 10 μ L of 65% acetonitrile/1% acetic acid is collected by the ZipTips and dispensed into a 96-well microtitre plate. 1 μ L of sample and 1 μ L of matrix are spotted on a MALDI-TOF sample
20 plate for analysis.

EXAMPLE 14 Mass Spectrometric Analysis of Interacting Proteins

(a) Method One for Analysis of Tryptic Peptides

Analytical samples containing tryptic peptides are subjected to Matrix Assisted
25 Laser Desorption/Ionization Time Of Flight (MALDI-TOF) mass spectrometry. Samples are mixed 1:1 with a matrix of α -cyano-4-hydroxy-*trans*-cinnamic acid. The sample/matrix mixture is spotted on to the MALDI sample plate with a robot. The sample/matrix mixture is allowed to dry on the plate and is then introduced into the mass spectrometer. Analysis of the peptides in the mass spectrometer is conducted using both delayed extraction mode
30 and an ion reflector to ensure high resolution of the peptides.

Internally-calibrated tryptic peptide masses are searched against both in-house proprietary and public databases using a correlative mass matching algorithm. Statistical

analysis is performed on each protein match to determine its validity. Typical search constraints include error tolerances within 0.1 Da for monoisotopic peptide masses and carboxyamidomethylation of cysteines. Identified proteins are stored automatically in a relational database with software links to SDS-PAGE images and ligand sequences.

5 (b) Method Two for Analysis of Tryptic Peptides

Alternatively, samples containing tryptic peptides are analyzed with an ion trap instrument. The peptide extracts are first dried down to approximately 1 μ L of liquid. To this, 0.1% trifluoroacetic acid (TFA) is added to make a total volume of approximately 5 μ L. Approximately 1-2 μ L of sample are injected onto a capillary column (C8, 150 μ m ID,
10 15 cm long) and run at a flow rate of 800 nL/min. using the following gradient program:

Time (minutes)	% Solvent A	% Solvent B
0	95	5
30	65	35
40	20	80
41	95	5

Where Solvent A is composed of water/0.5% acetic acid and Solvent B is acetonitrile/0.5% acetic acid. The majority of the peptides will elute between the 20-40 % acetonitrile gradient. Two types of data from the eluting HPLC peaks are acquired with the
15 ion trap mass spectrometer. In the MS¹ dimension, the mass to charge range for scanning is set at 400-1400 - this will determine the parent ion spectrum. Secondly, the instrument has MS² capabilities whereby it will acquire fragmentation spectra of any parent ions whose intensities are detected to be greater than a predetermined threshold (Mann and Wilm, *Anal Chem* 66(24): 4390-4399 (1994)). A significant amount of information is collected for each
20 protein sample as both a parent ion spectrum and many daughter ion spectra are generated with this instrumentation.

All resulting mass spectra are submitted to a database search algorithm for protein identification. A correlative mass algorithm is utilized along with a statistical verification of each match to identify a protein's identification (Ducret A, et al., *Protein Sci* 7(3): 706-
25 719 (1998)). This method proves much more robust than MALDI-TOF mass spectrometry for identifying the components of complex mixtures of proteins.

The identity of those interactor(s) are: ribosomal protein L23 (TIGR)-EF0208, ribosomal protein S3 (TIGR)-EF0212, ribosomal protein S5 (TIGR)-EF0224, ribosomal

protein L19 (TIGR)-EF1898, ribosomal protein S4 (TIGR)-EF3070 , ribosomal protein S2 (TIGR)-EF2398 , 22 and 30 kDa unidentified proteins.

EXAMPLE 15 NMR Analysis

5 Purified protein sample is centrifuged at 13,000 rpm for 10 minutes with a bench-top microcentrifuge to eliminate any precipitated protein. The supernatant is then transferred into a clean tube and the sample volume is measured. If the sample volume is less than 450 μ l, an appropriate amount of crystal buffer is added to the sample to reach that volume. Then 50 μ l of D₂O (99.9%) is added to the sample to make an NMR sample of
10 500 μ l. The usual concentration of the protein sample is usually approximately 1 mmol or greater.

NMR screening experiments are performed on a Bruker AV600 spectrometer equipped with a cryoprobe, or other equivalent instrumentation. All spectra are recorded at 25°C. Standard 1D proton pulse sequence with presaturation is used for 1D screening.
15 Normally, a sweepwidth of 6400 Hz, and eight or sixteen scans are used, although different pulse sequences are known to those of skill in the art and may be readily determined. For ¹H, ¹⁵N HSQC experiments, a pulse sequence with "flip-back" water suppression may be used. Typically, sweepwidths of 8000 Hz and 2000 Hz are used for F2 and F1 dimension, respectively. Four to sixteen scans are normally adequate. The data is then processed on a
20 Sun Ultra 5 computer with NMRpipe software.

EXAMPLE 16 X-ray Crystallography

(a) Crystallization

Suitable crystals for x-ray experimentation were obtained by vapor diffusion against
25 a 100 ml reservoir solution containing 11% PEG4000 as a precipitant, 2% ethylene glycol, 9% isopropanol, and 100mM HEPES pH 7.4 in a 96 well sitting plate format, setting 1.5 μ l 15 mg/ml protein and 1.5 μ l reservoir solutions in each drop. The crystals were soaked for 1 minute in a solution consisting of three parts mother liquor (from the well of the drop) to one part glycerol, and were then frozen at 100K in a cold gas stream. The crystal diffracted
30 to a minimum d-spacing of 2.3 Å.

(b) Co-Crystallization

A variety of methods known in the art may be used for preparation of co-crystals comprising a polypeptide of the invention and one or more compounds that interact with the subject polypeptides, such as, for example, an inhibitor, co-factor, substrate, polynucleotide, polypeptide, and/or other molecule. In one exemplary method, crystals of the subject polypeptide may be soaked, for an appropriate period of time, in a solution containing a compound that interacts with a subject polypeptide. In another method, solutions of the subject polypeptide and/or compound that interacts with the subject polypeptide may be prepared for crystallization as described above and mixed into the above-described sitting drops. In certain embodiments, the molecule to be co-crystallized with the subject polypeptide may be present in the buffer in the sitting drop prior to addition of the solution comprising the subject polypeptide. In other embodiments, the subject polypeptide may be mixed with another molecule before adding the mixture to the sitting drop. Based on the teachings herein, one of skill in the art may determine the co-crystallization method yielding a co-crystal comprising the subject polypeptide.

(c) Heavy Atom Substitution

For preparation of crystals containing heavy atoms, crystals of the subject polypeptide may be soaked in a solution of a compound containing the appropriate heavy atom for such period of time as may be experimentally determined is necessary to obtain a useful heavy atom derivative for x-ray purposes. Likewise, for other compounds that may be of interest, including, for example, inhibitors or other molecules that interact with the subject polypeptide, crystals of the subject polypeptide may be soaked in a solution of such compound for an appropriate period of time.

(d) Data collection and processing

Data was collected from these crystals at APS, Illinois, COMCAT beamline. All data were processed using the HKL2000 software package. Crystals proved to be of the orthorhombic space group $P2_12_12_1$ with cell dimensions $a = 76.434 \text{ \AA}$, $b = 112.876 \text{ \AA}$, $c = 125.792 \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$.

The *E. faecalis* *HisS* protein structure was solved by molecular replacement using the coordinates of the *Staphylococcus aureus* *HisS* dimer (PDB ID 1QE0; amino acid identity 47%) as the search model for molecular replacement using EPMR. Ten percent of the reflections were randomly excluded from the refinement, and used to monitor R_{free} in CNX. After rigid body refinement, an R_{free} of 49.4 % was obtained. After calculation of a density modified map, the structure was rebuilt using TURBO-FRODO (Roussel A. et

Cambillau C. (1989) TURBO-FRODO. Silicon Graphics Geometry Partner Directory, Silicon Graphics, Mountain view, California). A maximum likelihood target (with a flat bulk solvent correction and no low resolution or sigma cutoff applied to the data) was used in the refinement protocol. Refinement of the model using simulated annealing torsion
5 angle refinement and individual temperature factor refinement protocol was alternated with manual inspection and rebuilding of the model using TURBO-FRODO. After several cycles of refinement and manual rebuilding, most of the protein has been modeled for chain A, with only a few residues at the N- and C- termini being disordered. For chain B however, two substantial regions in addition, are disordered: residues 52 to 69, and residues
10 181:218. This latter stretch encompasses most of the helical insertion domain (Met169-Phe226), which appears to lack substantial intra-molecular contacts that might otherwise pin it into position. In addition to the protein chain, it was found that five additional residues are visible in the active site of chain A, and four are visible in the active site for chain B. Since at least some of these residues are clearly histidines, and the residues bind
15 in the histidine binding pocket, it would seem that the His tag from nearby symmetry related molecules span the solvent channel and are bound in the catalytic site. It should be noted that the exact identities of the side chains of residues beyond 1000-1002 is open to question; indeed, the self-similarity of the His-tag means that it is quite likely that there are several independent binding modes, where the His-tag binds with modes related by
20 displacing the tag 1 residue towards its N- or C- terminus. 121 solvent molecules were picked manually using a combination of sigma A weighted 2Fo-Fc and Fo-Fc maps.

Structure solution and refined statistics are reported in Table 3, contained in FIGURE 10. FIGURE 11 contains a list of the atomic coordinates of the subject polypeptide and other molecules contained in the crystal. FIGURE 12 to FIGURE 16
25 depict various features of the crystal structure and other properties of a subject polypeptide.

(e) Analysis of the X-ray Structure of the Subject Polypeptide

General Description of Structure

Like many other aminoacyl-tRNA synthetases, HisRS is active as a homodimer (FIGURE 13A). As with the *E. coli*, *S. aureus*, and *T. thermophilus* enzymes, the *E.*
30 *faecalis* HisRS monomer contains three domains (FIGURE 13B); the catalytic domain common to class II synthetases, the C-terminal domain most likely involved in binding the tRNA anticodon stem-loop, and a third α -helical domain inserted between motifs 2 and 3 in the catalytic domain. The C-terminal domain is connected to the catalytic domain by an

extended chain. The N-terminal catalytic domain (Met1-Asp168, Leu227-Glu319) has an eight-stranded β -sheet, with the central six strands forming the anti-parallel β -sheet that is conserved among all class II synthetases. The front of the β -sheet appears to be mostly open to allow substrate entry, while the back is well protected by helices and flanking loops (FIGURE 13B). The C-terminal subclass-defining domain (Leu330-Lys420) has a mixed five-stranded β -sheet and four helices. The helical insertion domain (Met169-Phe226) in the HisRS homo-dimer is ordered in one monomer (molecule A) but disordered in the other monomer.

In the dimer, the C-terminal domain of one subunit makes interactions exclusively with the catalytic domain of the other subunit. The two HisRS molecules in the dimer interact in a side by-side fashion with their C-terminal domains swapped (FIGURE 13A). One part of the dimer interface is between the catalytic domain of one monomer and the C-terminal domain of the other monomer. This interface is mostly hydrophilic. The other part of the interface is more hydrophobic and includes structural elements from the N-terminal loop (Met1-Leu12) and a small interface (SI) motif (Phe43-Leu77). The SI motif, shown in magenta in FIGURE 13B, is present in all class IIa synthetases. The two SI motifs interact intimately in the HisRS dimer, and the interaction is likely important for the HisRS mechanism.

Superposition of all the C α atoms of the backbone of the available HisRS structures demonstrates that the catalytic core is quite rigid, but that the peripheral domains are capable of considerable motion with respect to this platform. In general, the structures superimpose very closely, with "iterative magic fit" as implemented in Swiss pdb viewer giving an r.m.s.d. of 1.39 Å over 412 atoms. There is movement in the C terminal domain and in the insertion domain. The C-terminal domains undergo rigid body rotations of up to 8-15° (see, e.g., FIGURE 14), and the insertion domain appears capable of even more significant motions. The positions of the SI motifs in all the reported structures also move slightly. Since the SI motif involves both the active site and the dimer interface, the observed conformational change may implicate a communicational path between the two active sites of the dimer.

The most significant ligand-induced conformational changes occur in the histidine binding pocket (FIGURE 15). In the ligand bound structures, the binding pocket is a narrow cavity that is more than 20 Å deep. Atoms lining the pocket provide an intricate network of hydrogen bonding interactions as well as van der Waals contacts with the

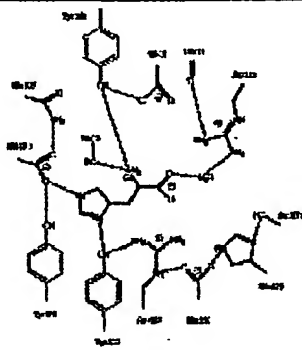
substrate histidine. The changes seen in the apo *S. aureus* structure are centered at the HisA motif loop (257-RGLDYY-262) and the wide open pocket appears to require notable conformational changes to form a complementary binding pocket for histidine. In the *E. faecalis* structure, a polypeptide containing at least three consecutive histidine residues is found in binding pocket; presumably these residues correspond to the histidine tag. Although the tag was not cleaved, the C-terminus of symmetry related molecules can be found 18 and 21 Å away for the N-terminus of the peptides in the A and B monomers' binding sites respectively, a distance easily spanned by the fourteen to sixteen residues missing from the electron density map. An overlay of the *T. thermophilus* histidine bound structure with the *E. faecalis* structure shows some differences in the orientation of the side chain residues (FIGURE 15D).

Several important loops in the active site either become disordered or adopt very different conformations compared to their ligand-bound states. Such loops may comprising druggable regions. These include the histidine A motif (Arg257-Tyr262) that appears essential for substrate recognition, a loop (Gly52-Lys62) that seems to control the communication between the histidine and ATP binding sites, the motif 2 loop (Glu114-Arg120) that binds ATP, and the insertion domain that is likely to bind tRNA. These ligand-induced structural changes are supported by fluorescence experiments, which also suggest highly cooperative dynamics. A dynamic and cooperative active site is most likely necessary for the proper functioning of the histidyl-tRNA synthetase, and suggests a novel mechanism for improving charging fidelity.

Active Site and Other Druggable Regions

In the ligand-bound HisRS structures, the histidine-binding pocket seems to be optimized to utilize the hydrogen bonding capabilities of as well as shape and electrostatic complementarity to histidine. The histidine-binding pocket may comprise a druggable region. The active site residues, which may comprise a druggable region, appear to be highly conserved in HisRS (FIGURE 16). An alignment shows a high degree of sequence conservation along the length of the polypeptide chain amongst HisRS proteins from several pathogenic bacterial species (FIGURE 12). Table 4 describes the conserved active site residues for the histidine-ATP binding pocket. The HisRS specific peptides 259-RGLDYY and 287-GGRYNG (in *E. faecalis* and *S. aureus*; 285-GGRYDG in *T. thermophilus*, *E. coli*, *H. influenzae*, *P. aeruginosa* and *S. pneumoniae*) form a specific pocket where histidine is buried.

Table 4: Active site residues for HisRS in different species

<u>Binding Site Identifier</u>	<i>E. faecalis</i>	<i>E. coli</i>	<i>T. thermophilus</i>	<i>S. aureus</i>	<u>Description of Binding Site</u>
<u>Binding Site I: Histidine</u>	P80 E81 T83 R114 G130 E132 R259 Y263 Y264 E270 M272 S282 Y290	P82 E83 T85 R113 G129 E131 R259 Y263 Y264 E270 V272 G280 Y288	P80 E81 T83 R112 N128 E130 R259 Y263 Y264 E270 H272 S280 Y288	P79 E80 T82 R112 G128 E130 R257 Y261 Y262 E268 M270 T281 Y289	 <p>Figure of <i>T. thermophilus</i> histidine binding site from Aberg et al., 1997</p>
<u>Binding Site II: ATP</u>	F126 E116 L123 I129carbonyl R114 R259	F125 E115 Y122 T12carbonyl R113 R259	F124 E114 Y121 V127carbonyl R112 R259	F124 E114 Y121 F127carbonyl R112 R257	ATP is selected over other purines. R259 is important for catalysis. R259 and R113 are unique to Syh since they replace metal ions coordinating the phosphates.
<u>HisA motif</u>	259RDL GYY264	259R DLG YY264	259RDLGY Y264	257RDL GYY262	essential arginine in the HisA motif was observed to bind the R-phosphate and lies near the histidine carboxylate and is a likely catalytic residue, replacing the essential divalent metal ion (Mg ²⁺) in other class II tRNA synthetases
<u>HisB motif</u>	287GG RYNGL 293	285G GRY DGL 291	285GGRYD GL291	286GGR YNGL292	Important when binding histidine

Hence, binding sites I and II, or subsets of the residues comprising them, may comprise a druggable region, as may the HisA and B motif regions or subsets of residues comprising them.

5 Known Inhibitors of Histidine tRNA synthetases

Many analogs of histidine have been tested for their properties as substrates or inhibitors of HisRS, leading to the elucidation of structure-activity relationships concerning configuration, importance of the carboxy and amino group, and the nature of the side chain.

Histidinol has been co-crystallized with ATP in *E. coli* HisRS (PDB ID 1KMN). ATP analogues have also been tested as substrates or inhibitors of HisRS.

Comparison to Other Histidine tRNA synthetases

Crystal structures of *Escherichia coli* HisRS in complex with histidyl-adenylate or with histidinol and ATP have been reported; as have *Thermus thermophilus* structures in complexes with histidine or with histidyl-adenylate. They all contain the class II and subclass IIa signature modules: the antiparallel β -sheet catalytic domain and the C-terminal anticodon-binding domain. A 60-residue insertion domain, in position to bind the tRNA acceptor stem, is visible in the *T. thermophilus* structures but is disordered in the *E. coli* structures. The HisA and HisB motifs interact intimately with the substrate histidine. The essential arginine in the HisA motif was observed to bind the R-phosphate and lies near the histidine carboxylate. The arginine is a likely catalytic residue, replacing the essential divalent metal ion (Mg^{2+}) in other class II tRNA synthetases. Comparisons of the crystal structure of the apo *Staphylococcus aureus* histidyl-tRNA synthetase and ligand-bound structures reveal considerable conformational changes in the active site. These changes are ligand induced and presumed to occur in a highly cooperative fashion. The magnitude of the movement in HisRS is greater than any previously reported for tRNA synthetases.

Based in part on the structural information described above, in one aspect, the present invention is directed towards druggable regions of a subject polypeptide or other histidine tRNA synthetase comprising the majority of the amino acid residues contained in any of the above-described druggable regions. In another aspect, the present invention is directed toward an modulator or that interacts with an active or binding site of a histidine tRNA synthetase. In one embodiment, this site is binding site I of Table 4. In certain embodiments, the ADP/ATP binding site may be comprised of at least one of P80, E81, T83, R114, G130, E132, R259, Y263, Y264, E270, M272, S282, or Y290. In another embodiment, this site is binding site II of Table 4. In certain embodiments, the GMP binding site may be comprised of at least one of F126, E116, L123, I129carbonyl, R114, or R259. In another aspect, the present invention is directed towards an modulator that interacts with a loop of a histidine tRNA synthetase so as to modulate its movement, thereby modulating the activity of such enzyme. In certain embodiments, the loop is comprised of at least one residue selected from the group of loops consisting of: the HisA motif, the His B motif, the Gly52-Lys62 loop, and the insertion domain that is likely to bind tRNA.

EXAMPLE 17 Annotations

The functional annotation is arrived at by comparing the amino acid sequence of the ORF against all available ORFs in the NCBI database using BLAST. The closest match is selected to provide the probable function of the polypeptide having the sequence of SEQ ID NO: 2. Results of this comparison are described above and set forth in Table 2 of FIGURE 7.

The COGs database (Tatusov RL, Koonin EV, Lipman DJ. Science 1997; 278 (5338) 631-37) classifies proteins encoded in twenty-one completed genomes on the basis of sequence similarity. Members of the same Cluster of Orthologous Group, ("COG"), are expected to have the same or similar domain architecture and the same or substantially similar biological activity. The database may be used to predict the function of uncharacterised proteins through their homology to characterized proteins. The COGs database may be searched from NCBI's website (<http://www.ncbi.nlm.nih.gov/COG/>) to determine functional annotation descriptions, such as "information storage and processing" (translation, ribosomal structure and biogenesis, transcription, DNA replication, recombination and repair); "cellular processes" (cell division and chromosome partitioning, post-translational modification, protein turnover, chaperones, cell envelope biogenesis, outer membrane, cell motility and secretion, inorganic ion transport and metabolism, signal transduction mechanisms); or "metabolism" (energy production and conversion, carbohydrate transport and metabolism, amino acid transport and metabolism, nucleotide transport and metabolism, coenzyme metabolism, lipid metabolism). For certain polypeptides, there is no entry available. Results of this analysis are described above and set forth in Table 2 of FIGURE 7.

EXAMPLE 18 Essential Gene Analysis

SEQ ID NO: 2 is compared to a number of publicly available "essential genes" lists to determine whether that protein is encoded by an essential gene. An example of such a list is descended from a free release at the www.shigen.nig.ac.jp PEC (profiling of *E. coli* chromosome) site, <http://www.shigen.nig.ac.jp/ecoli/pec/>. The list is prepared as follows: a wildcard search for all genes in class "essential" yields the list of essential *E. coli* proteins encoded by essential genes, which number 230. These 230 hits are pruned by comparing against an NCBI *E. coli* genome. Only 216 of the 230 genes on the list are found in the

NCBI genome. These 216 are termed the essential-216-ecoli list. The essential-216-ecoli list is used to garner "essential" genes lists for other microbial genomes by blasting. For instance, formatting the 216-ecoli as a BLAST database, then BLASTing a genome (e.g. *S. aureus*) against it, elucidates all *S. aureus* genes with significant homology to a gene in the 216-essential list. SEQ ID NO: 2 is compared against the appropriate list and a match with a score of e^{-25} or better is considered an essential gene according to that list. In addition to the list described above, other lists of essential genes are publicly available or may be determined by methods disclosed publicly, and such lists and methods are considered in deciding whether a gene is essential. See, for example, Thanassi et al., Nucleic Acids Res 2002 Jul 15;30(14):3152-62; Forsyth et al., Mol Microbiol 2002 Mar;43(6):1387-400; Ji et al., Science 2001 Sep 21;293(5538):2266-9; Sasseti et al., Proc Natl Acad Sci U S A 2001 Oct 23;98(22):12712-7; Reich et al., J Bacteriol 1999 Aug;181(16):4961-8; Akerley et al., Proc Natl Acad Sci U S A 2002 Jan 22;99(2):966-71). Also, other methods are known in the art for determining whether a gene is essential, such as that disclosed in U.S. Patent Application No. 10/202,442 (filed July 24, 2002). The conclusion as to whether the gene encoding the amino acid sequence set forth in SEQ ID NO: 2 is essential is set forth in Table 2 of FIGURE 7.

EXAMPLE 19 PDB Analysis

SEQ ID NO: 2 is compared against the amino acid sequences in a database of proteins whose structures have been solved and released to the PDB (protein data bank). The identity/information about the top PDB homolog (most similar "hit", if any; a PDB entry is only considered a hit if the score is e^{-4} or better) is annotated, and the percent similarity and identity between SEQ ID NO: 2 and the closest hit is calculated, with both being indicated in Table 2 of FIGURE 7.

EXAMPLE 20 Virtual Genome Analysis

VGDB or VG is a queryable collection of microbial genome databases annotated with biophysical and protein information. The organisms present in VG include:

File	GRAM	Species	Source	Genome file date
ecoli.faa	G-	<i>Escherichia coli</i>	NCBI	November 18 1998
hpyl.faa	G-	<i>Helicobacter pylori</i>	NCBI	April 19 1999
paer.faa	G-	<i>Pseudomonas aeruginosa</i>	NCBI	September 22 2000

ctra.faa	G-	<i>Chlamydia trachomatis</i>	NCBI	December 22 1999
hinf.faa	G-	<i>Haemophilus influenzae</i>	NCBI	November 26 1999
nmen.faa	G-	<i>Neisseria meningitidis</i>	NCBI	December 28 2000
rpax.faa	G-	<i>Rickettsia prowazekii</i>	NCBI	December 22 1999
bbur.faa	G-	<i>Borrelia burgdorferi</i>	NCBI	November 11 1998
bsub.faa	G+	<i>Bacillus subtilis</i>	NCBI	December 1 1999
staph.faa	G+	<i>Staphylococcus aureus</i>	TIGR	March 8 2001
		<i>Streptococcus</i>		
spne.faa	G+	<i>pneumoniae</i>	TIGR	February 22 2001
mgen.faa	G+	<i>Mycoplasma genitalium</i>	NCBI	November 23 1999
efac.faa	G+	<i>Enterococcus faecalis</i>	TIGR	March 8 2001

The VGDB comprises 13 microbial genomes, annotated with biophysical information (pI, MW, etc), and a wealth of other information. These 13 organism genomes are stored in a single flatfile (the VGDB) against which PSI-blast queries can be done.

5 SEQ ID NO: 2 is queried against the VGDB to determine whether this sequence is found, conserved, in many microbial genomes. There are certain criteria that must be met for a positive hit to be returned (beyond the criteria inherent in a basic PSI-blast).

When an ORF is queried it may have a maximum of 13 VG-organism hits. A hit is classified as such as long as it matches the following criteria: Minimum Length (as
10 percentage of query length): 75 (*Ensure hit protein is at least 75% as long as query*); Maximum Length (as percentage of query length): 125 (*Ensure hit protein is no more than 125% as long as query*); eVal:-10 (*Ensure hit has an e-Value of e-10 or better*); Id%:>:25 (*Ensure hit protein has at least 25% identity to query*). The e-Value is a standard parameter of BLAST sequence comparisons, and represents a measure of the similarity between two
15 sequences based on the likelihood that any similarities between the two sequences could have occurred by random chance alone. The lower the e-Value, the less likely that the similarities could have occurred randomly and, generally, the more similar the two sequences are.

20 The organisms having an orthologue of the polypeptide having SEQ ID NO: 2 are listed in Table 2, shown in FIGURE 7.

EXAMPLE 21 Epitopic Regions

The three most likely epitopic regions of a polypeptide having SEQ ID NO: 2 are predicted using the semi-empirical method of Kolaskar and Tongaonkar (FEBS Letters
25 1990 v276 172-174), the software package called Protean (DNASTAR), or MacVectors's

Protein analysis tools (Accerlyrs). The antigenic propensity of each amino acid is calculated by the ratio between frequency of occurrence of amino acids in 169 antigenic determinants experimentally determined and the calculated frequency of occurrence of amino acids at the surface of protein. The results of these bioinformatics analyses are presented in Table 2, shown in FIGURE 7.

EQUIVALENTS

The present invention provides among other things, novel proteins, protein structures and protein-protein interactions. While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control. To the extent that any U.S. Provisional Patent Applications to which this patent application claims priority incorporate by reference another U.S. Provisional Patent Application, such other U.S. Provisional Patent Application is not incorporated by reference herein unless this patent application expressly incorporates by reference, or claims priority to, such other U.S. Provisional Patent Application.

Also incorporated by reference in their entirety are any polynucleotide and polypeptide sequences which reference an accession number correlating to an entry in a public database, such as those maintained by The Institute for Genomic Research (TIGR) (www.tigr.org) and/or the National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov).

Also incorporated by reference are the following: WO 00/45168, WO 00/79238, WO 00/77712, EP 1047108, EP 1047107, WO 00/72004, WO 00/73787, WO00/67017, WO 00/48004, WO 01/48209, WO 00/45168, WO 00/45164, U.S.S.N. 09/720272; PCT/CA99/00640; U.S. Patent Application Nos: 10/097125 (filed March 12, 2002); 10/097193 (filed March 12, 2002); 10/202442 (filed July 24, 2002); 10/097194 (filed

March 12, 2002); 09/671817 (filed September 17, 2000); 09/965654 (filed September 27, 2001); 09/727812 (filed November 30, 2000); 60/370667 (filed April 8, 2002); a utility patent application entitled "Methods and Apparatuses for Purification" (filed September 18, 2002); U.S. Patent Numbers 6451591; 6254833; 6232114; 6229603; 6221612; 6214563; 5 6200762; 6171780; 6143492; 6124128; 6107477; D428157; 6063338; 6004808; 5985214; 5981200; 5928888; 5910287; 6248550; 6232114; 6229603; 6221612; 6214563; 6200762; 6197928; 6180411; 6171780; 6150176; 6140132; 6124128; 6107066; 6270988; 6077707; 6066476; 6063338; 6054321; 6054271; 6046925; 6031094; 6008378; 5998204; 5981200; 5955604; 5955453; 5948906; 5932474; 5925558; 5912137; 5910287; 5866548; 6214602; 10 5834436; 5777079; 5741657; 5693521; 5661035; 5625048; 5602258; 5552555; 5439797; 5374710; 5296703; 5283433; 5141627; 5134232; 5049673; 4806604; 4689432; 4603209; 6217873; 6174530; 6168784; 6271037; 6228654; 6184344; 6040133; 5910437; 5891993; 5854389; 5792664; 6248558; 6341256; 5854922; and 5866343.

Aberg, A., et al. (1997) *Biochemistry*, 36, 3084-3094; Arnez, J. G., et al. (1997) 15 *Proc. Natl Acad. Sci. USA*, 94, 7144-7149; Arnez, J. G., et al. (1995) *EMBO J.* 14, 4143-4155; Francklyn, C., et al. (1990) *Proc. Natl. Acad. Sci. U.S.A.* 87, 8655-8659; Francklyn, C., et al. (1992) *Science* 255, 1121-1125; Freist W, et al. (1999) *Biol Chem.* 380, 623-46; Himeno, H., et al. (1989) *Nucleic Acids Res.* 19, 7855-7863; Nameki, N., et al. (1995) *Nucleic Acid Res.* 23, 389-394; Qiu, X., et al. (1999) *Biochemistry*, 38, 12296-12304; 20 Steinberg, S., et al. (1993) *Nucleic Acids Res.* 21, 3011-3015; Xiayang Qiu, et al. (1999) *Biochemistry* 38, 12296-12304; Yan, W., et al. (1994) *J. Biol. Chem.* 269, 10022-10027.

We claim:

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CLAIMS

1. A composition comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID
5 NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of *histidine tRNA synthetase* from *E. faecalis*; and wherein
10 the polypeptide of (a), (b) or (c) is at least about 90% pure in a sample of the composition.

2. The composition of claim 1, wherein the polypeptide is at least about 95% pure as determined by gel electrophoresis.

3. The composition of claim 1, wherein the polypeptide is purified to essential homogeneity.

15 4. The composition of claim 1, wherein at least about two-thirds of the polypeptide in the sample is soluble.

5. The composition of claim 1, wherein the polypeptide is fused to at least one heterologous polypeptide that increases the solubility or stability of the polypeptide.

6. The composition of claim 1, which further comprises a matrix suitable for mass
20 spectrometry.

7. The composition of claim 6, wherein the matrix is a nicotinic acid derivative or a cinnamic acid derivative.

8. A sample comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID
25 NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of *histidine tRNA synthetase* from *E. faecalis*; and wherein
30 the polypeptide of (a), (b) or (c) is labeled with a heavy atom.

9. The sample of claim 8, wherein the heavy atom is one of the following: cobalt, selenium, krypton, bromine, strontium, molybdenum, ruthenium, rhodium, palladium, silver, cadmium, tin, iodine, xenon, barium, lanthanum, cerium, praseodymium,

neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, lutetium, tantalum, tungsten, rhenium, osmium, iridium, platinum, gold, mercury, thallium, lead, thorium and uranium.

10. The sample of claim 8, wherein the polypeptide is labeled with seleno-methionine.

11. The sample of claim 8, further comprising a cryo-protectant.

12. The sample of claim 11, wherein the cryo-protectant is one of the following: methyl pentanediol, isopropanol, ethylene glycol, glycerol, formate, citrate, mineral oil and a low-molecular-weight polyethylene glycol.

13. A crystallized, recombinant polypeptide comprising: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; wherein the polypeptide of (a), (b) or (c) is in crystal form.

14. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 13 and a co-factor, wherein the complex is in crystal form.

15. A crystallized complex comprising the crystallized, recombinant polypeptide of claim 13 and a small organic molecule, wherein the complex is in crystal form.

16. The crystallized, recombinant polypeptide of claim 13, which diffracts x-rays to a resolution of about 3.5 Å or better.

17. The crystallized, recombinant polypeptide of claim 13, wherein the polypeptide comprises at least one heavy atom label.

18. The crystallized, recombinant polypeptide of claim 17, wherein the polypeptide is labeled with seleno-methionine.

19. A method for designing a modulator for the prevention or treatment of *E. faecalis* related disease or disorder, comprising:

(a) providing a three-dimensional structure for a crystallized, recombinant polypeptide of claim 13;

(b) identifying a potential modulator for the prevention or treatment of *E. faecalis* related disease or disorder by reference to the three-dimensional structure;

(c) contacting a polypeptide of the composition of claim 1 or *E. faecalis* with the potential modulator; and

(d) assaying the activity of the polypeptide or determining the viability of *E. faecalis* after contact with the modulator, wherein a change in the activity of the polypeptide or the viability of *E. faecalis* indicates that the modulator may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

20. A sample comprising an isolated, recombinant polypeptide, wherein the polypeptide comprises: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and wherein the polypeptide of (a), (b) or (c) is enriched in at least one NMR isotope.

21. The sample of claim 20, wherein the NMR isotope is one of the following: hydrogen-1 (^1H), hydrogen-2 (^2H), hydrogen-3 (^3H), phosphorous-31 (^{31}P), sodium-23 (^{23}Na), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), carbon-13 (^{13}C) and fluorine-19 (^{19}F).

22. The sample of claim 20, further comprising a deuterium lock solvent.

23. The sample of claim 22, wherein the deuterium lock solvent is one of the following: acetone (CD_3COCD_3), chloroform (CDCl_3), dichloro methane (CD_2Cl_2), methyl nitrile (CD_3CN), benzene (C_6D_6), water (D_2O), diethylether ($(\text{CD}_3\text{CD}_2)_2\text{O}$), dimethylether ($(\text{CD}_3)_2\text{O}$), N,N-dimethylformamide ($(\text{CD}_3)_2\text{NCDO}$), dimethyl sulfoxide (CD_3SOCD_3), ethanol ($\text{CD}_3\text{CD}_2\text{OD}$), methanol (CD_3OD), tetrahydrofuran ($\text{C}_4\text{D}_8\text{O}$), toluene ($\text{C}_6\text{D}_5\text{CD}_3$), pyridine ($\text{C}_5\text{D}_5\text{N}$) and cyclohexane (C_6H_{12}).

24. The sample of claim 20, which is contained within an NMR tube.

25. A method for identifying small molecules that bind to a polypeptide of the composition of claim 1, comprising:

(a) generating a first NMR spectrum of an isotopically labeled polypeptide of the composition of claim 1;

(b) exposing the polypeptide to one or more small molecules;

(c) generating a second NMR spectrum of the polypeptide which has been exposed to one or more small molecules; and

(d) comparing the first and second spectra to determine differences between the first and the second spectra, wherein the differences are indicative of one or more small molecules that have bound to the polypeptide.

26. A host cell comprising a nucleic acid encoding a polypeptide comprising: (a) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (b) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (c) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; wherein a culture of the host cell produces at least about 1 mg of the polypeptide per liter of culture and the polypeptide is at least about one-third soluble as measured by gel electrophoresis.

27. An isolated, recombinant polypeptide, comprising: (a) an amino acid sequence having at least about 90% identity with the amino acid sequence set forth in SEQ ID NO: 4; or (b) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and wherein the polypeptide comprises one or more of the following amino acid residues at the specified position of the polypeptide: P80, E81, T83, R114, G130, E132, R259, Y263, Y264, E270, M272, S282, or Y290.

28. A method for obtaining structural information of a crystallized polypeptide, the method comprising:

(a) crystallizing a recombinant polypeptide, wherein the polypeptide comprises: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and wherein the crystallized polypeptide is capable of diffracting X-rays to a resolution of 3.5 Å or better; and

(b) analyzing the crystallized polypeptide by X-ray diffraction to determine the three-dimensional structure of at least a portion of the crystallized polypeptide.

29. The method of claim 28, wherein the three-dimensional structure of the portion of the crystallized polypeptide is determined to a resolution of 3.5 Å or better.

30. A method for identifying a druggable region of a polypeptide, the method comprising:

5 (a) obtaining crystals of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ
10 ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*, such that the three dimensional structure of the crystallized polypeptide may be determined to a resolution of 3.5 Å or better;

(b) determining the three dimensional structure of the crystallized polypeptide using X-ray diffraction; and

15 (c) identifying a druggable region of the crystallized polypeptide based on the three-dimensional structure of the crystallized polypeptide.

31. The method of claim 30, wherein the druggable region is an active site.

32. The method of claim 31, wherein the druggable region is on the surface of the polypeptide.

20 33. Crystalline histidine tRNA synthetase from *E. faecalis* comprising a crystal having unit cell dimensions $a = 76.434 \text{ Å}$, $b = 112.876 \text{ Å}$, $c = 125.792 \text{ Å}$, $\alpha = \beta = \gamma = 90^\circ$ and space group $P2_12_12_1$.

34. A crystallized polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95%
25 identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of *histidine tRNA synthetase* from *E. faecalis*; wherein the crystal has a $P2_12_12_1$ space group.

30 35. A crystallized polypeptide comprising a structure of a polypeptide that is defined by a substantial portion of the atomic coordinates set forth in FIGURE 11.

36. A method for determining the crystal structure of a homolog of a polypeptide, the method comprising:

- (a) providing the three dimensional structure of a first crystallized polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of *histidine tRNA synthetase* from *E. faecalis*;
- (b) obtaining crystals of a second polypeptide comprising an amino acid sequence that is at least 70% identical to the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4, such that the three dimensional structure of the second crystallized polypeptide may be determined to a resolution of 3.5 Å or better; and
- (c) determining the three dimensional structure of the second crystallized polypeptide by x-ray crystallography based on the atomic coordinates of the three dimensional structure provided in step (a).

37. The method of claim 36, wherein the atomic coordinates for the second crystallized polypeptide have a root mean square deviation from the backbone atoms of the first polypeptide of not more than 1.5 Å for all backbone atoms shared in common with the first polypeptide and the second polypeptide.

38. A method for homology modeling a homolog of histidine tRNA synthetase from *E. faecalis*, comprising:

- (a) aligning the amino acid sequence of a homolog of histidine tRNA synthetase from *E. faecalis* with an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and incorporating the sequence of the homolog of histidine tRNA synthetase from *E. faecalis* into a model of histidine tRNA synthetase from *E. faecalis* derived from structure coordinates as listed in FIGURE 11 to yield a preliminary model of the homolog of histidine tRNA synthetase from *E. faecalis*;
- (b) subjecting the preliminary model to energy minimization to yield an energy minimized model;

(c) remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the homolog of histidine tRNA synthetase from *E. faecalis*.

39. A method for obtaining structural information about a molecule or a molecular
5 complex of unknown structure comprising:

(a) crystallizing the molecule or molecular complex;

(b) generating an x-ray diffraction pattern from the crystallized molecule or molecular complex;

(c) applying at least a portion of the structure coordinates set forth in FIGURE 11 to
10 the x-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

40. A method for attempting to make a crystallized complex comprising a polypeptide and a modulator having a molecular weight of less than 5 kDa, the method comprising:

15 (a) crystallizing a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ
20 ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; such that crystals of the crystallized polypeptide will diffract x-rays to a resolution of 5 Å or better; and

(b) soaking the crystals in a solution comprising a potential modulator having a molecular weight of less than 5 kDa.

25 41. A method for incorporating a potential modulator in a crystal of a polypeptide, comprising placing a crystal of histidine tRNA synthetase from *E. faecalis* having unit cell dimensions $a = 76.434 \text{ Å}$, $b = 112.876 \text{ Å}$, $c = 125.792 \text{ Å}$, $\alpha = \beta = \gamma = 90^\circ$ and space group $P2_12_12_1$, in a solution comprising the potential modulator.

42. A computer readable storage medium comprising digitally encoded structural
30 data, wherein the data comprises structural coordinates as listed in FIGURE 11 for the backbone atoms of at least about six amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis*.

43. A scalable three-dimensional configuration of points, at least a portion of the points derived from some or all of the structure coordinates as listed in FIGURE 11 for a plurality of amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis*.

5 44. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the backbone atoms of at least about five amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points.

10 45. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the backbone and optionally the side chain atoms of at least about ten amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points.

15 46. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the backbone atoms of at least about fifteen amino acid residues from a druggable region of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points.

47. The scalable three-dimensional configuration of points of claim 43, wherein substantially all of the points are derived from structure coordinates as listed in FIGURE 11.

20 48. The scalable three-dimensional configuration of points of claim 43, wherein the structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* are used to derive part or all of the portion of points:

25 49. A scalable three-dimensional configuration of points, comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the backbone atoms of at least five amino acid residues, wherein the five amino acid residues are from a druggable region of histidine tRNA synthetase from *E. faecalis*.

30 50. The scalable three-dimensional configuration of points of claim 49, wherein any point-to-point distance, calculated from the three dimensional coordinates as listed in FIGURE 11, between one of the backbone atoms for one of the five amino acid residues and another backbone atom of a different one of the five amino acid residues is not more than about 10 Å.

51. A scalable three-dimensional configuration of points comprising points having a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis*:

5 52. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise the identity and three-dimensional coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis*:

10 53. A scalable three-dimensional configuration of points, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis*, wherein up to one amino acid residue in each of the regions may have a conservative substitution thereof.

15 54. A scalable three-dimensional configuration of points derived from a druggable region of a polypeptide, wherein the points have a root mean square deviation of less than about 1.5 Å from the three dimensional coordinates as listed in FIGURE 11 for the backbone atoms of at least ten amino acid residues that participate in the intersubunit contacts of histidine tRNA synthetase from *E. faecalis*.

20 55. A computer-assisted method for identifying an inhibitor of the activity of histidine tRNA synthetase from *E. faecalis*, comprising:

(a) supplying a computer modeling application with a set of structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* so as to define part or all of a molecule or complex;

25 (b) supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

(c) determining whether the chemical entity is expected to bind to or interfere with the molecule or complex.

30 56. The method of claim 55, wherein determining whether the chemical entity is expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

57. The method of claim 55, further comprising screening a library of chemical entities.

58. A computer-assisted method for designing an inhibitor of histidine tRNA synthetase activity comprising:

- 5 (a) supplying a computer modeling application with a set of structure coordinates having a root mean square deviation of less than about 1.5 Å from the structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* so as to define part or all of a molecule or complex;
- 10 (b) supplying the computer modeling application with a set of structure coordinates for a chemical entity;
- (c) evaluating the potential binding interactions between the chemical entity and the molecule or complex;
- (d) structurally modifying the chemical entity to yield a set of structure coordinates
15 for a modified chemical entity; and
- (e) determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of histidine tRNA synthetase activity.

20 59. The method of claim 58, wherein determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and the molecule or complex, followed by computationally analyzing the results of the fitting operation to evaluate the association between the chemical entity and the molecule or complex.

25 60. The method of claim 58, wherein the set of structure coordinates for the chemical entity is obtained from a chemical library.

61. A computer-assisted method for designing an inhibitor of histidine tRNA synthetase activity *de novo* comprising:

- 30 (a) supplying a computer modeling application with a set of three-dimensional coordinates derived from the structure coordinates as listed in FIGURE 11 for the atoms of the amino acid residues from any of the above-described druggable regions of histidine tRNA synthetase from *E. faecalis* so as to define part or all of a molecule or complex;

(b) computationally building a chemical entity represented by a set of structure coordinates; and

(c) determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of histidine tRNA synthetase activity.

62. The method of claim 61, wherein determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or complex comprises performing a fitting operation between the chemical entity and a druggable region of the molecule or complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the druggable region.

63. The method of any of claims 55, 58 or 61, further comprising supplying or synthesizing the potential inhibitor, then assaying the potential inhibitor to determine whether it inhibits histidine tRNA synthetase activity.

64. A method for identifying a potential modulator for the prevention or treatment of a *E. faecalis* related disease or disorder, the method comprising:

(a) providing the three dimensional structure of a crystallized polypeptide comprising: (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*;

(b) obtaining a potential modulator for the prevention or treatment of *E. faecalis* related disease or disorder based on the three dimensional structure of the crystallized polypeptide;

(c) contacting the potential modulator with a second polypeptide comprising: (i) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (ii) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (iii) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine

tRNA synthetase from *E. faecalis*; which second polypeptide may optionally be the same as the crystallized polypeptide; and

- (d) assaying the activity of the second polypeptide, wherein a change in the activity of the second polypeptide indicates that the compound may be useful for prevention or treatment of a *E. faecalis* related disease or disorder.

65. A method for designing a candidate modulator for screening for inhibitors of a polypeptide, the method comprising:

- (a) providing the three dimensional structure of a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*; and

- (b) designing a candidate modulator based on the three dimensional structure of the druggable region of the polypeptide.

66. A method for identifying a potential modulator of a polypeptide from a database, the method comprising:

- (a) providing the three-dimensional coordinates for a plurality of the amino acids of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*;

- (b) identifying a druggable region of the polypeptide; and

(c) selecting from a database at least one potential modulator comprising three dimensional coordinates which indicate that the modulator may bind or interfere with the druggable region.

67. The method of claim 66, wherein the modulator is a small molecule.

68. A method for preparing a potential modulator of a druggable region contained in a polypeptide, the method comprising:

- 5 (a) using the atomic coordinates for the backbone atoms of at least about six amino acid residues from a polypeptide of SEQ ID NO: 4, with a \pm a root mean square deviation from the backbone atoms of the amino acid residues of not more than 1.5 Å, to generate one or more three-dimensional structures of a molecule comprising a druggable region from the polypeptide;
- (b) employing one or more of the three dimensional structures of the molecule to design or select a potential modulator of the druggable region; and
- 10 (c) synthesizing or obtaining the modulator.

69. An apparatus for determining whether a compound is a potential modulator of a polypeptide, the apparatus comprising:

- (a) a memory that comprises:
 - 15 (i) the three dimensional coordinates and identities of at least about fifteen atoms from a druggable region of a polypeptide comprising (1) an amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; (2) an amino acid sequence having at least about 95% identity with the amino acid sequence set forth in SEQ ID NO: 2 or SEQ ID NO: 4; or (3) an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of a polynucleotide having SEQ ID NO: 1 or SEQ
 - 20 ID NO: 3 and has at least one biological activity of histidine tRNA synthetase from *E. faecalis*;
 - (ii) executable instructions; and
- (b) a processor that is capable of executing instructions to:
 - (i) receive three-dimensional structural information for a candidate
 - 25 modulator;
 - (ii) determine if the three-dimensional structure of the candidate modulator is complementary to the three dimensional coordinates of the atoms from the druggable region; and
 - (iii) output the results of the determination.

- 30 70. A method for making an inhibitor of histidine tRNA synthetase activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield an

inhibitor of histidine tRNA synthetase activity, the chemical entity having been identified during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or complex, the molecule or complex comprising at least a portion of at least one druggable region from histidine tRNA synthetase from *E. faecalis*; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind or to interfere with the molecule or complex at a druggable region, wherein binding to or interfering with the molecule or complex is indicative of potential inhibition of histidine tRNA synthetase activity.

10 71. A computer readable storage medium comprising digitally encoded data, wherein the data comprises structural coordinates for a druggable region that is structurally homologous to the structure coordinates as listed in FIGURE 11 for a druggable region of histidine tRNA synthetase from *E. faecalis*.

15 72. A computer readable storage medium comprising digitally encoded structural data, wherein the data comprise a majority of the three-dimensional structure coordinates as listed in FIGURE 11.

73. The computer readable storage medium of claim 72, further comprising the identity of the atoms for the majority of the three-dimensional structure coordinates as listed in FIGURE 11.

20 74. The computer readable storage medium of claim 72, wherein the data comprise substantially all of the three-dimensional structure coordinates as listed in FIGURE 11.

FIGURE 1

SEQ ID NO: 1

ATGAGTTATCAAAAACCAAAGGAACAAACGATATTTTGCCAGGAACCTTCTGA
5 AAAATGGCAATTTGTGGAAGAAACAGCTCGTTTGATTTTTAAAGATTATCAATACCAAG
AAATCAGAACCCCGATTTTGAACATTATGAAGTAATATCTCGCAGTGTTGGCGATACC
ACAGATATTGTTTCAAAAGAAATGTATGATTTTTATGATAAAGGAGACCGTCACGTGAC
GCTACGTCCTGAGGGGACAGCGCCAATTGTTTCGGGCCTTCGTTGAAAATAAATTATATG
GTCCGGAATATACGAAACCATATAAAACCTATTACATGGGGCCGATGTTCCGCTATGA
10 ACGCCCAAGCTGGTCGTTTGCCTCAATTCATCAAATTGGTGTGGAAGCATTGTTGTA
GTGAAAACCCAGCATTGGATGTTGAAATCATGGCTATGGCTTTGGACTTCTTCAAACAA
TTAGGCATCCAACAAATCAAATTAGTTATTAATTCCTTGGGGGATAAAGAAACACGTG
CTACGTACCGTCAAGCATTAAATCGATTATTTAGAGCCCCATATGGCAGAATTAAGCGAG
GATTCACAACGTCGCTTACACGAAAACCCATTGCGGGTGTTAGACAGCAAAGATAAAA
15 AAGACAAGGTGATTGTCGAGAAGCGCCCTCCATTTTGGATTATTTAAATGAACCATCT
AAAGCACATTTTGAAGCAGTAACTGATATGTTAGATTTACTAGAAATTCCTTATGAAAT
TGATAGTAATATGGTTCGTGGCCTGGATTATTATACACACACAATTTTGAATTATGA
GTGAAGCGCCTAAAATGGGTGCGCAATCAACTATTTGTGCAGGAGGCCGATACAATGG
TTTAGTTGAAGAATTAGGCGGCCAGACACACCAGGTTTTGGTTTTGGTATGGGCATTG
20 AGCGAGTGTTGTTAACAATGGAAGCTGAAGAAGTTGTGATTCCAGCGTTATCTGAATTA
GACGCATATGTGGTTGGGATTGGTTCAGACACCAACGTCGCAGCTTTGCAACTTGTTC
AAGCATTTCGTAACCTTTGGTTTCTCAGCTGATCGTGATTACATGAATCGCAAACCAAAAG
CGCAATTTAAACGGCCGATAAATTACAAGCAAAATTAGTTTTAACAATCGGTGAAAA
TGAATTGAATGAAGGCATTGTCAACGTAAAATCAATGGCAACACGCGAAGAAAAAGCC
25 TTCCCGTTAAGTGCTATTCATGATTCATTTGATGAAGTGATGACGAAATGATGACAAA
AATGATTGAAGAATGA

FIGURE 2

SEQ ID NO: 2

MSYQKPKGTDILPGTSEKWQFVEETARLIFKDYQYQEIRTPIFEHYEVISRSVGDTT
5 DIVSKEMYDFYDKGDRHVTLRPEGTAPIVRAFVENKLYGPEYTKPYKTYYMGPMPFRYERP
QAGRLRQFHQIGVEAFGSENPALDVEIMAMALDFFKQLGIQQIKLVINSLGDKETRATYRQ
ALIDYLEPHMAELSEDSQRRLENPLRVLDSKDKKDKVIVAEAPSILDYLNESKAHFEAVT
DMLDLLEIPYEIDSNMVRGLDYYTHTIFEIMSEAPKMGAQSTICAGGRYNGLVEELGGPDTP
GFGFGMGIERVLLTMEAEVVIPALSELDAYVVGIGSDTNVAALQLVQSIRNFGFSADRDY
10 MNRKPKAQFKTADKLQAKLVLTIGENELNEGIVNVKSMATREEKAFPLSAIHDSFDEVYDE
MMTKMIEE

FIGURE 3

SEQ ID NO: 3

ATGAGTTATCAAAAACCAAAAGGAACAAACGATATTTTGCCAGGAACTTCTGA
5 AAAATGGCAATTTGTGGAAGAAACAGCTCGTTTGATTTTTAAAGATTATCAATACCAAG
AAATCAGAACCCCGATTTTTGAACATTATGAAGTAATATCTCGCAGTGTTGGCGATACC
ACAGATATTGTTTCAAAAGAAATGTATGATTTTTATGATAAAGGAGACCGTCAACGTGAC
GCTACGTCCTGAGGGGACAGCGCCAATTGTTCTGGGCCTTCGTTGAAAATAAATTATATG
GTCCGGGATATACGAAACCATATAAAACCTATTACGTGGGGCCGATGTTCCGCTATGA
10 ACGCCCAAGCTGGTCGTTTGCGTCAATTCCATCAAATTGGTGTGGAAGCGTTTGGTA
GTGGAAACCCACCATTTGGATGTTGAAATCATGGCTATGGCTTTGGACTTCTTCAAACAA
TTAGGCATCCAACAAATCAAATTAATTATTAATTCCTTGGGGGATAAAGAAACACGTG
CTACGTACCGTCCAGCATTAATCGATTATTTAGAGCCCCATATGGCAGAATTAAGCGAG
GATTCAACGTCGCTTACACGAAAACCCATTGCGGGTGTTAGACAGCAAAGATAAAA
15 AAGACAAGGTGATTGTGCGAGAAGCGCCCTCCATTTTGGATTATTTAAATGAACCATCT
AAAGCACATTTTGAAGCAGTAACTGATATGTTAGATTTACTAGAAATTCCTTATGAAAT
TGATAGTAATATGGTTCGTGGCCTGGATTATTATACACACACAATTTTGAATTAGGA
GTGAAGCGCTTAAAAATGGGTGCGCAATCAACTATTTGTGCAGGAGGCCGATACAATGG
TTTAGTTGAAGAATTAGGCGGCCAGACACACCAGGTTTTGGTTTTGGTATGGGCATTG
20 AGCGAGTGTTGTTAACAATGGAAGCTGAAGAAGTTGTGATTCCAGCGTTATCTGAATTA
GACGCATATGTGGTTGGGATTGGTTCAGACACCAACGTCGCAGCTTTGCAACTTGTTC
AAGCATTCGTAACCTTTGGTTTCTCAGCTGATCGTGATTACATGAATCGCAAACCAAAAG
CGCAATTTAAACGGCCGATAAATTACAAGCAAAATTAGTTTTAACAATCGGTGAAAA
TGAATTGAATGAAGGCATTGTCAACGTAAAATCAATGGCAACACGCGAAGAAAAAGCC
25 TTCCCGTTAAGTGCTATTCATGATTCATTTGATGAAGTGTATGACGAAATGATGACAAA
AATGATTGAAGAATGA

FIGURE 4

SEQ ID NO: 4

MSYQKPKGTNDILPGTSEK WQFVEETARLIFKDYQYQEIRTPIFEHYEVISRSVGDTT
5 DIVSKEMYDFYDKGDRHVTLRPEGTAPIVRAFVENKLYGPGYTKPYKTYVVGPMFRYERP
QAGRLRQFHQIGVEAFGSGNPPLDVEIMAMALDFFKQLGIQQIKLIINSLGDKETRATYRPA
LIDYLEPHMAELSEDSQRRLENPLRVLDSKDKKDKVIVAEAPSILDYLNESKAHFEAVTD
MLDLLEIPYEIDSNMVRGLDYYTHTIFEIRSEALKMGAQSTICAGGRYNGLVEELGGPDTPG
FGFGMGIERVLLTMEAEVVIPALSELDAYVVGIGSDTNVAALQLVQSIRNFGFSADRDYM
10 NRKPKAQFKTADKLQAKLVL TIGENELNEGIVNVKSMATREEKAFPLSAIHDSFDEVYDEM
MTKMIEE

FIGURE 5

SEQ ID NO: 5

Forward PCR Primer

5 CGCGGGGTACCATGAGTTATCAAAAACCAAAAGG

10 SEQ ID NO: 6

Reverse PCR Primer

GCGCGGATCCTTCAATCATTTTTGTCATCATTC

15

FIGURE 6

TABLE 1: Amino Acid and Nucleic Acid Properties

Melting temperature (°C) of SEQ ID NO: 5 (forward PCR primer)	60
Restriction enzyme for SEQ ID NO: 5 (forward PCR primer)	KpnI
Melting temperature (°C) of SEQ ID NO: 6 (reverse PCR primer)	60
Restriction enzyme for SEQ ID NO: 6 (reverse PCR primer)	BamHI
Number of nucleic acid residues in SEQ ID NO: 1	1302
Number of amino acid residues in SEQ ID NO: 2	433
Number of different nucleic acid residues between SEQ ID NO: 1 and SEQ ID NO: 3	9
Number of different amino acid residues between SEQ ID NO: 2 and SEQ ID NO: 4	8
Calculated molecular weight of SEQ ID NO: 2 polypeptide (kDa)	49.273
Calculated pI of SEQ ID NO: 2 polypeptide	4.5
Solubility of SEQ ID NO: 4 polypeptide, determined as described in EXAMPLE 2 (with the His tag at the N-terminus)	Approaching 100%
Solubility of SEQ ID NO: 4 polypeptide, determined as described in EXAMPLE 2 (with the His tag at the C-terminus)	Approaching 100%
Amount of purified polypeptide having SEQ ID NO: 4, prepared and purified as described in EXAMPLE 8 (mg/L of culture)	31.03
Amount of purified polypeptide having SEQ ID NO: 4 soluble in buffer, as described in EXAMPLE 8 (mg/ml of buffer)	21.40
Z-score for the peptide fingerprint mapping analysis, determined as described in EXAMPLE 9	2.41
Number of matched peptides in the peptide fingerprint mapping analysis, determined as described in EXAMPLE 9	14
Minimum sequence coverage in the peptide fingerprint mapping analysis, determined as described in EXAMPLE 9	31%
Calculated molecular weight of SEQ ID NO: 2 polypeptide (Da), determined as described in EXAMPLE 10	51089
Experimental molecular weight of SEQ ID NO: 2 polypeptide (Da), determined as described in EXAMPLE 10	51031

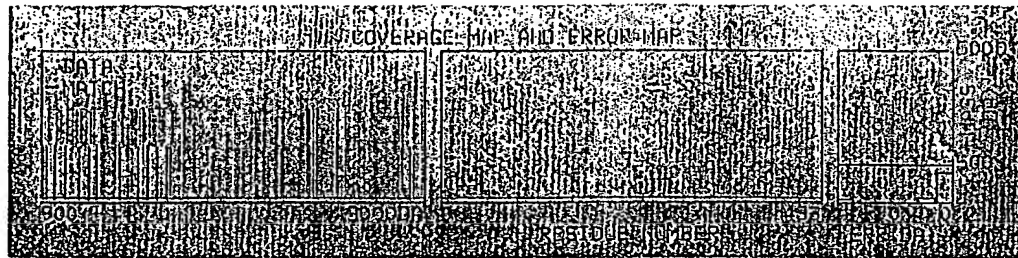
FIGURE 7

TABLE 2: Bioinformatic Analyses

Protein annotation and gene designation, if any	histidine tRNA synthetase, <i>hisS</i>
COG Category	Translation, ribosomal structure and biogenesis
COG ID Number	COG0124
Is SEQ ID NO: 2 classified as an essential gene?	yes
Most closely related protein from PDB	Histidyl-tRNA Synthetase, (1qe0)
Source organism for closest PDB protein	<i>Staphylococcus aureus</i>
e-value for closest PDB Protein	1.00E-118
% Identity between SEQ ID NO: 2 and the closest protein from PDB	48
% Positives between SEQ ID NO: 2 and the closest protein from PDB	66
Number of Protein Hits in the VGDB	11
Number of Microorganisms having VGDB Hits	11
Microorganisms having VGDB Hits ¹	ecoli nmen saur rpro efae ctra hinf spne bsub paer mgen
First predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.201,343->353, SEQ ID NO:7 NVAALQLVQSI
Second predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.187,321->339, SEQ ID NO:8 EEVVIPALSELDAYVVGIG
Third predicted epitopic region of SEQ ID NO: 2: rank score, amino acid residue numbers; amino acid sequence	1.163,378->387, SEQ ID NO:9 KLQAKLVLTl

- ¹Organisms are abbreviated as follows: ecoli = *Eschericia coli*; hpyl = *Helicobacter pylori*; paer = *Pseudomonas aeruginosa*; ctra = *Chlaydia trachomatis*; hinf = *Haemophilus influenzae*; nmen = *Neisseria meningitidis*; rpxx = *Rickettsia prowazekii*; bbur = *Borrelia burgdorferi*; bsub = *Bacillus subtilis*; staph = *Staphylococcus aureus*; spne = *Streptococcus pneumoniae*; mgen = *Mycoplasma genitalium*; efae = *Enterococcus faecalis*.

FIGURE 8



Measured Mass (M)	Avg/ Mono	Computed Mass	Error (Da)	Residues Start	Missed To	Cut	Peptide sequence
912.604	M	912.409	0.195	355	362	0	NFGFSADR
926.742	M	926.554	0.188	155	162	0	OLGIQIQIK
975.659	M	975.488	0.171	115	122	0	YERPQAGR
1033.729	M	1033.578	0.151	199	206	1	KLHGNFLR
1113.659	M	1113.509	0.151	33	40	0	DYQYQEI
1164.687	M	1164.509	0.178	106	114	0	TYMGPFR
1164.687	M	1164.556	0.131	20	28	0	WQVESTAR
1207.709	M	1207.543	0.166	278	289	0	NGAQSTICAGGR
1343.887	M	1343.740	0.147	163	174	1	LVINSLGDKETR
1437.725	M	1437.586	0.139	64	74	1	EHYDFYDKQDR
1489.896	M	1489.756	0.140	41	52	0	TRIPENYEIVSR
1545.024	M	1544.878	0.146	75	88	0	HVTLRPEGTAPIVR
1591.828	M	1591.683	0.145	355	367	1	NFGFSADRDYNNR
1614.981	M	1614.840	0.142	29	40	1	LIFKDYQYQEI
2920.241	M	2920.397	-0.156	235	259	0	AHFEAVTDHLDLLEIPYEIDSNMVR

FIGURE 9

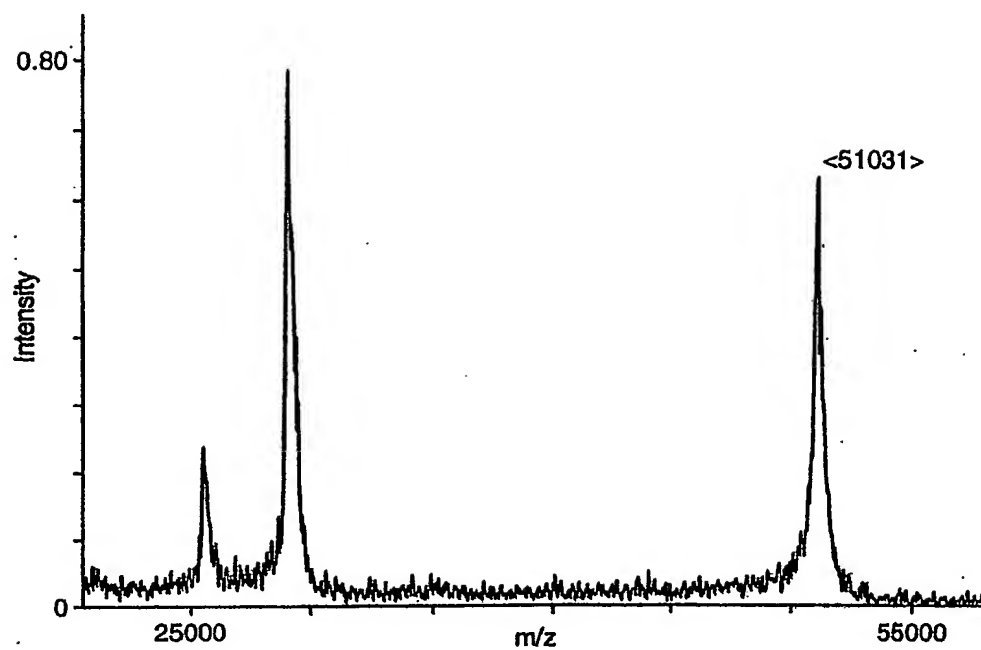


FIGURE 10

TABLE 3: X-ray Structure Data

(a) Data Collection	
Wavelength	1.0
Space group	P2 ₁ 2 ₁ 2 ₁
Unit cell dimensions	a = 76.434 Å b = 122.876 Å c = 125.792 Å; $\alpha = \beta = \gamma = 90^\circ$
Resolution range (Å)	20 - 2.3
Completeness (%) ^{a,b}	94.2(89.6)
I/ σ I	23(2.7)
R _{merge}	5.1(30.8)
Number of reflections: Total	314403
Unique	50355
(b) Structure Refinement	
R _{cryst} ^d	27.3
R _{free}	23.4
Number of atoms	
protein	6315
solvent	133
Average B-factors	
protein (Å ²)	57.9
solvent (Å ²)	52.6
R.M.S. Deviations from ideal	
Bond (Å)	0.007
Angle (°)	1.28
^a Number in parentheses is the statistic for highest resolution shell. ^b $I \geq \sigma I$ ^c $R_{\text{sym}} = \sum_h (\sum_j I_{j,h} - \langle I_h \rangle / \sum_j I_{j,h})$, where h = set of Miller indices and j = set of observations of reflection h. ^d $R_{\text{cryst}} = \sum_{hkl} F_o - F_c / \sum_{hkl} F_o $	

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FIGURE 11

ATOM	1	CB	THR	A	9	82.065	149.640	59.961	1.00	68.18	A	C
ATOM	2	OG1	THR	A	9	81.103	150.585	60.460	1.00	71.65	A	O
ATOM	3	CG2	THR	A	9	83.371	149.794	60.749	1.00	66.04	A	C
ATOM	4	C	THR	A	9	80.947	149.889	57.751	1.00	64.05	A	C
ATOM	5	O	THR	A	9	80.020	150.589	58.164	1.00	63.15	A	O
ATOM	6	N	THR	A	9	82.982	151.211	58.232	1.00	67.94	A	N
ATOM	7	CA	THR	A	9	82.303	149.899	58.454	1.00	66.43	A	C
ATOM	8	N	ASN	A	10	80.834	149.103	56.686	1.00	61.00	A	N
ATOM	9	CA	ASN	A	10	79.577	149.019	55.958	1.00	57.40	A	C
ATOM	10	CB	ASN	A	10	79.837	148.810	54.473	1.00	61.29	A	C
ATOM	11	CG	ASN	A	10	80.243	150.086	53.774	1.00	64.80	A	C
ATOM	12	OD1	ASN	A	10	81.290	150.663	54.063	1.00	67.11	A	O
ATOM	13	ND2	ASN	A	10	79.405	150.541	52.851	1.00	66.47	A	N
ATOM	14	C	ASN	A	10	78.706	147.893	56.482	1.00	53.96	A	C
ATOM	15	O	ASN	A	10	77.916	147.319	55.738	1.00	53.22	A	O
ATOM	16	N	ASP	A	11	78.860	147.579	57.766	1.00	49.07	A	N
ATOM	17	CA	ASP	A	11	78.083	146.523	58.393	1.00	44.34	A	C
ATOM	18	CB	ASP	A	11	78.794	145.982	59.635	1.00	44.30	A	C
ATOM	19	CG	ASP	A	11	80.239	145.633	59.378	1.00	44.73	A	C
ATOM	20	OD1	ASP	A	11	80.503	144.807	58.489	1.00	48.60	A	O
ATOM	21	OD2	ASP	A	11	81.117	146.183	60.070	1.00	45.61	A	O
ATOM	22	C	ASP	A	11	76.737	147.078	58.830	1.00	41.76	A	C
ATOM	23	O	ASP	A	11	76.612	148.269	59.118	1.00	39.58	A	O
ATOM	24	N	ILE	A	12	75.740	146.206	58.882	1.00	37.14	A	N
ATOM	25	CA	ILE	A	12	74.409	146.588	59.323	1.00	36.54	A	C
ATOM	26	CB	ILE	A	12	73.358	146.099	58.302	1.00	36.24	A	C
ATOM	27	CG2	ILE	A	12	71.939	146.424	58.784	1.00	36.81	A	C
ATOM	28	CG1	ILE	A	12	73.636	146.792	56.957	1.00	38.34	A	C
ATOM	29	CD1	ILE	A	12	72.892	146.217	55.784	1.00	39.91	A	C
ATOM	30	C	ILE	A	12	74.270	145.936	60.706	1.00	35.40	A	C
ATOM	31	O	ILE	A	12	74.127	144.721	60.836	1.00	34.70	A	O
ATOM	32	N	LEU	A	13	74.345	146.772	61.735	1.00	35.22	A	N
ATOM	33	CA	LEU	A	13	74.316	146.341	63.135	1.00	35.02	A	C
ATOM	34	CB	LEU	A	13	75.269	147.235	63.944	1.00	32.45	A	C
ATOM	35	CG	LEU	A	13	76.664	147.353	63.339	1.00	32.19	A	C
ATOM	36	CD1	LEU	A	13	77.474	148.420	64.054	1.00	30.72	A	C
ATOM	37	CD2	LEU	A	13	77.328	145.998	63.411	1.00	30.95	A	C
ATOM	38	C	LEU	A	13	72.968	146.356	63.834	1.00	35.24	A	C
ATOM	39	O	LEU	A	13	72.009	146.946	63.352	1.00	33.73	A	O
ATOM	40	N	PRO	A	14	72.886	145.692	64.996	1.00	38.29	A	N
ATOM	41	CD	PRO	A	14	73.825	144.685	65.531	1.00	38.32	A	C
ATOM	42	CA	PRO	A	14	71.624	145.676	65.739	1.00	40.38	A	C
ATOM	43	CB	PRO	A	14	71.991	144.918	67.005	1.00	39.68	A	C
ATOM	44	CG	PRO	A	14	72.937	143.870	66.474	1.00	37.76	A	C
ATOM	45	C	PRO	A	14	71.234	147.125	66.008	1.00	42.45	A	C
ATOM	46	O	PRO	A	14	72.066	147.925	66.439	1.00	43.56	A	O
ATOM	47	N	GLY	A	15	69.980	147.474	65.734	1.00	43.90	A	N
ATOM	48	CA	GLY	A	15	69.547	148.848	65.939	1.00	44.20	A	C
ATOM	49	C	GLY	A	15	69.144	149.460	64.608	1.00	46.63	A	C
ATOM	50	O	GLY	A	15	68.249	150.310	64.540	1.00	48.41	A	O
ATOM	51	N	THR	A	16	69.817	149.053	63.536	1.00	43.84	A	N
ATOM	52	CA	THR	A	16	69.445	149.557	62.234	1.00	42.13	A	C
ATOM	53	CB	THR	A	16	70.608	150.303	61.522	1.00	42.92	A	C
ATOM	54	OG1	THR	A	16	71.442	149.367	60.845	1.00	48.08	A	O
ATOM	55	CG2	THR	A	16	71.445	151.084	62.530	1.00	42.75	A	C
ATOM	56	C	THR	A	16	69.009	148.357	61.411	1.00	39.21	A	C
ATOM	57	O	THR	A	16	68.188	148.481	60.499	1.00	38.90	A	O
ATOM	58	N	SER	A	17	69.527	147.184	61.754	1.00	36.19	A	N

FIGURE 11-11

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ATOM	59	CA	SER	A	17	69.164	145.996	61.002	1.00	36.72	A	C
ATOM	60	CB	SER	A	17	69.946	144.765	61.487	1.00	35.11	A	C
ATOM	61	OG	SER	A	17	69.534	144.336	62.762	1.00	38.23	A	O
ATOM	62	C	SER	A	17	67.661	145.765	61.097	1.00	35.40	A	C
ATOM	63	O	SER	A	17	67.061	145.196	60.184	1.00	34.17	A	O
ATOM	64	N	GLU	A	18	67.052	146.230	62.189	1.00	35.27	A	N
ATOM	65	CA	GLU	A	18	65.608	146.087	62.373	1.00	35.54	A	C
ATOM	66	CB	GLU	A	18	65.171	146.495	63.787	1.00	39.03	A	C
ATOM	67	CG	GLU	A	18	65.560	145.507	64.856	1.00	47.64	A	C
ATOM	68	CD	GLU	A	18	67.057	145.517	65.135	1.00	52.65	A	C
ATOM	69	OE1	GLU	A	18	67.550	144.532	65.742	1.00	52.19	A	O
ATOM	70	OE2	GLU	A	18	67.726	146.515	64.756	1.00	52.83	A	O
ATOM	71	C	GLU	A	18	64.861	146.950	61.368	1.00	32.37	A	C
ATOM	72	O	GLU	A	18	63.743	146.630	60.985	1.00	32.84	A	O
ATOM	73	N	LYS	A	19	65.468	148.056	60.960	1.00	29.45	A	N
ATOM	74	CA	LYS	A	19	64.835	148.926	59.987	1.00	29.61	A	C
ATOM	75	CB	LYS	A	19	65.597	150.244	59.882	1.00	32.28	A	C
ATOM	76	CG	LYS	A	19	65.627	150.998	61.219	1.00	37.74	A	C
ATOM	77	CD	LYS	A	19	66.337	152.329	61.128	1.00	38.04	A	C
ATOM	78	CE	LYS	A	19	66.329	153.024	62.480	1.00	38.26	A	C
ATOM	79	NZ	LYS	A	19	66.731	154.450	62.353	1.00	42.24	A	N
ATOM	80	C	LYS	A	19	64.810	148.201	58.653	1.00	30.98	A	C
ATOM	81	O	LYS	A	19	63.779	148.171	57.970	1.00	31.46	A	O
ATOM	82	N	TRP	A	20	65.942	147.602	58.294	1.00	27.27	A	N
ATOM	83	CA	TRP	A	20	66.024	146.855	57.063	1.00	28.18	A	C
ATOM	84	CB	TRP	A	20	67.392	146.195	56.919	1.00	28.59	A	C
ATOM	85	CG	TRP	A	20	68.451	147.159	56.531	1.00	28.84	A	C
ATOM	86	CD2	TRP	A	20	69.066	147.274	55.251	1.00	28.72	A	C
ATOM	87	CE2	TRP	A	20	69.951	148.363	55.316	1.00	29.99	A	C
ATOM	88	CE3	TRP	A	20	68.947	146.567	54.047	1.00	27.90	A	C
ATOM	89	CD1	TRP	A	20	68.969	148.142	57.296	1.00	26.65	A	C
ATOM	90	NE1	TRP	A	20	69.869	148.872	56.581	1.00	28.97	A	N
ATOM	91	CZ2	TRP	A	20	70.728	148.774	54.221	1.00	31.05	A	C
ATOM	92	CZ3	TRP	A	20	69.718	146.972	52.954	1.00	29.88	A	C
ATOM	93	CH2	TRP	A	20	70.599	148.069	53.053	1.00	28.23	A	C
ATOM	94	C	TRP	A	20	64.950	145.790	57.089	1.00	30.28	A	C
ATOM	95	O	TRP	A	20	64.186	145.655	56.137	1.00	30.38	A	O
ATOM	96	N	GLN	A	21	64.889	145.039	58.187	1.00	31.70	A	N
ATOM	97	CA	GLN	A	21	63.897	143.980	58.329	1.00	31.66	A	C
ATOM	98	CB	GLN	A	21	63.975	143.356	59.716	1.00	33.15	A	C
ATOM	99	CG	GLN	A	21	65.057	142.295	59.876	1.00	36.22	A	C
ATOM	100	CD	GLN	A	21	65.510	142.162	61.321	1.00	36.21	A	C
ATOM	101	OE1	GLN	A	21	64.729	142.376	62.244	1.00	36.03	A	O
ATOM	102	NE2	GLN	A	21	66.773	141.805	61.521	1.00	36.94	A	N
ATOM	103	C	GLN	A	21	62.479	144.471	58.102	1.00	31.48	A	C
ATOM	104	O	GLN	A	21	61.693	143.815	57.433	1.00	31.20	A	O
ATOM	105	N	PHE	A	22	62.152	145.621	58.668	1.00	30.77	A	N
ATOM	106	CA	PHE	A	22	60.818	146.162	58.525	1.00	29.48	A	C
ATOM	107	CB	PHE	A	22	60.655	147.384	59.420	1.00	28.47	A	C
ATOM	108	CG	PHE	A	22	59.354	148.105	59.228	1.00	30.37	A	C
ATOM	109	CD1	PHE	A	22	58.150	147.523	59.618	1.00	31.57	A	C
ATOM	110	CD2	PHE	A	22	59.329	149.365	58.667	1.00	29.20	A	C
ATOM	111	CE1	PHE	A	22	56.940	148.191	59.453	1.00	27.20	A	C
ATOM	112	CE2	PHE	A	22	58.115	150.045	58.498	1.00	31.63	A	C
ATOM	113	CZ	PHE	A	22	56.923	149.448	58.897	1.00	27.64	A	C
ATOM	114	C	PHE	A	22	60.537	146.541	57.071	1.00	31.86	A	C
ATOM	115	O	PHE	A	22	59.414	146.385	56.589	1.00	33.16	A	O
ATOM	116	N	VAL	A	23	61.542	147.059	56.374	1.00	31.48	A	N
ATOM	117	CA	VAL	A	23	61.344	147.435	54.983	1.00	30.27	A	C
ATOM	118	CB	VAL	A	23	62.534	148.228	54.437	1.00	28.40	A	C
ATOM	119	CG1	VAL	A	23	62.467	148.293	52.897	1.00	26.74	A	C

FIGURE 11-12

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ATOM	120	CG2	VAL	A	23	62.530	149.611	55.028	1.00	27.24	A	C
ATOM	121	C	VAL	A	23	61.164	146.188	54.135	1.00	31.67	A	C
ATOM	122	O	VAL	A	23	60.322	146.140	53.242	1.00	32.85	A	O
ATOM	123	N	GLU	A	24	61.958	145.172	54.425	1.00	31.69	A	N
ATOM	124	CA	GLU	A	24	61.891	143.939	53.672	1.00	35.03	A	C
ATOM	125	CB	GLU	A	24	63.101	143.067	54.006	1.00	33.12	A	C
ATOM	126	CG	GLU	A	24	64.413	143.723	53.591	1.00	34.98	A	C
ATOM	127	CD	GLU	A	24	65.632	143.124	54.285	1.00	38.12	A	C
ATOM	128	OE1	GLU	A	24	65.466	142.252	55.172	1.00	39.09	A	O
ATOM	129	OE2	GLU	A	24	66.759	143.531	53.942	1.00	39.16	A	O
ATOM	130	C	GLU	A	24	60.594	143.189	53.920	1.00	36.61	A	C
ATOM	131	O	GLU	A	24	60.020	142.623	52.993	1.00	35.81	A	O
ATOM	132	N	GLU	A	25	60.115	143.201	55.161	1.00	38.85	A	N
ATOM	133	CA	GLU	A	25	58.879	142.503	55.462	1.00	39.77	A	C
ATOM	134	CB	GLU	A	25	58.683	142.338	56.969	1.00	41.27	A	C
ATOM	135	CG	GLU	A	25	57.771	141.171	57.326	1.00	48.33	A	C
ATOM	136	CD	GLU	A	25	58.436	139.796	57.127	1.00	55.92	A	C
ATOM	137	OE1	GLU	A	25	59.178	139.598	56.125	1.00	59.88	A	O
ATOM	138	OE2	GLU	A	25	58.205	138.901	57.978	1.00	58.51	A	O
ATOM	139	C	GLU	A	25	57.695	143.254	54.862	1.00	38.94	A	C
ATOM	140	O	GLU	A	25	56.737	142.641	54.392	1.00	40.83	A	O
ATOM	141	N	THR	A	26	57.750	144.578	54.869	1.00	36.51	A	N
ATOM	142	CA	THR	A	26	56.656	145.344	54.293	1.00	34.24	A	C
ATOM	143	CB	THR	A	26	56.857	146.846	54.493	1.00	32.50	A	C
ATOM	144	OG1	THR	A	26	56.777	147.148	55.886	1.00	32.26	A	O
ATOM	145	CG2	THR	A	26	55.797	147.631	53.758	1.00	32.72	A	C
ATOM	146	C	THR	A	26	56.553	145.030	52.801	1.00	35.06	A	C
ATOM	147	O	THR	A	26	55.459	144.882	52.273	1.00	34.83	A	O
ATOM	148	N	ALA	A	27	57.697	144.923	52.128	1.00	35.26	A	N
ATOM	149	CA	ALA	A	27	57.708	144.603	50.705	1.00	36.62	A	C
ATOM	150	CB	ALA	A	27	59.151	144.614	50.140	1.00	28.17	A	C
ATOM	151	C	ALA	A	27	57.082	143.222	50.521	1.00	36.82	A	C
ATOM	152	O	ALA	A	27	56.144	143.066	49.736	1.00	34.82	A	O
ATOM	153	N	ARG	A	28	57.597	142.231	51.252	1.00	37.34	A	N
ATOM	154	CA	ARG	A	28	57.075	140.868	51.159	1.00	38.66	A	C
ATOM	155	CB	ARG	A	28	57.749	139.942	52.194	1.00	39.18	A	C
ATOM	156	CG	ARG	A	28	59.213	139.598	51.885	1.00	43.03	A	C
ATOM	157	CD	ARG	A	28	59.811	138.634	52.906	1.00	44.91	A	C
ATOM	158	NE	ARG	A	28	61.266	138.504	52.770	1.00	52.87	A	N
ATOM	159	CZ	ARG	A	28	61.891	138.030	51.688	1.00	54.87	A	C
ATOM	160	NH1	ARG	A	28	61.197	137.629	50.622	1.00	54.99	A	N
ATOM	161	NH2	ARG	A	28	63.217	137.957	51.666	1.00	52.87	A	N
ATOM	162	C	ARG	A	28	55.550	140.796	51.323	1.00	38.29	A	C
ATOM	163	O	ARG	A	28	54.869	140.144	50.534	1.00	36.09	A	O
ATOM	164	N	LEU	A	29	55.016	141.463	52.341	1.00	38.77	A	N
ATOM	165	CA	LEU	A	29	53.578	141.436	52.581	1.00	40.34	A	C
ATOM	166	CB	LEU	A	29	53.248	142.115	53.917	1.00	40.41	A	C
ATOM	167	CG	LEU	A	29	53.929	141.319	55.051	1.00	47.65	A	C
ATOM	168	CD1	LEU	A	29	53.702	141.971	56.420	1.00	47.08	A	C
ATOM	169	CD2	LEU	A	29	53.399	139.880	55.040	1.00	46.65	A	C
ATOM	170	C	LEU	A	29	52.804	142.067	51.435	1.00	40.26	A	C
ATOM	171	O	LEU	A	29	51.865	141.452	50.912	1.00	40.00	A	O
ATOM	172	N	ILE	A	30	53.205	143.273	51.029	1.00	39.33	A	N
ATOM	173	CA	ILE	A	30	52.543	143.959	49.921	1.00	38.33	A	C
ATOM	174	CB	ILE	A	30	53.223	145.304	49.571	1.00	40.25	A	C
ATOM	175	CG2	ILE	A	30	52.633	145.855	48.282	1.00	37.36	A	C
ATOM	176	CG1	ILE	A	30	53.011	146.329	50.688	1.00	43.73	A	C
ATOM	177	CD1	ILE	A	30	51.648	147.009	50.668	1.00	44.18	A	C
ATOM	178	C	ILE	A	30	52.586	143.104	48.658	1.00	37.41	A	C
ATOM	179	O	ILE	A	30	51.583	142.931	47.982	1.00	36.88	A	O
ATOM	180	N	PHE	A	31	53.763	142.580	48.346	1.00	37.40	A	N

FIGURE 11-13

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ATOM	181	CA	PHE	A	31	53.963	141.777	47.151	1.00	39.36	A	C
ATOM	182	CB	PHE	A	31	55.444	141.430	47.014	1.00	37.73	A	C
ATOM	183	CG	PHE	A	31	56.291	142.597	46.647	1.00	35.28	A	C
ATOM	184	CD1	PHE	A	31	57.660	142.578	46.868	1.00	35.82	A	C
ATOM	185	CD2	PHE	A	31	55.722	143.721	46.074	1.00	37.21	A	C
ATOM	186	CE1	PHE	A	31	58.445	143.654	46.528	1.00	30.09	A	C
ATOM	187	CE2	PHE	A	31	56.505	144.810	45.730	1.00	36.64	A	C
ATOM	188	CZ	PHE	A	31	57.872	144.772	45.961	1.00	34.06	A	C
ATOM	189	C	PHE	A	31	53.122	140.516	47.110	1.00	41.49	A	C
ATOM	190	O	PHE	A	31	52.589	140.157	46.059	1.00	41.51	A	O
ATOM	191	N	LYS	A	32	53.013	139.841	48.249	1.00	42.27	A	N
ATOM	192	CA	LYS	A	32	52.207	138.635	48.327	1.00	44.22	A	C
ATOM	193	CB	LYS	A	32	52.355	137.987	49.710	1.00	47.19	A	C
ATOM	194	CG	LYS	A	32	51.635	136.648	49.856	1.00	54.13	A	C
ATOM	195	CD	LYS	A	32	51.912	135.982	51.211	1.00	57.81	A	C
ATOM	196	CE	LYS	A	32	53.326	135.409	51.284	1.00	61.24	A	C
ATOM	197	NZ	LYS	A	32	53.556	134.324	50.274	1.00	62.33	A	N
ATOM	198	C	LYS	A	32	50.733	138.982	48.038	1.00	42.38	A	C
ATOM	199	O	LYS	A	32	50.070	138.280	47.281	1.00	42.93	A	O
ATOM	200	N	ASP	A	33	50.227	140.066	48.620	1.00	40.40	A	N
ATOM	201	CA	ASP	A	33	48.841	140.467	48.384	1.00	41.81	A	C
ATOM	202	CB	ASP	A	33	48.458	141.670	49.263	1.00	43.40	A	C
ATOM	203	CG	ASP	A	33	48.322	141.311	50.741	1.00	48.05	A	C
ATOM	204	OD1	ASP	A	33	48.402	140.111	51.080	1.00	48.73	A	O
ATOM	205	OD2	ASP	A	33	48.128	142.236	51.568	1.00	51.80	A	O
ATOM	206	C	ASP	A	33	48.568	140.818	46.907	1.00	42.21	A	C
ATOM	207	O	ASP	A	33	47.424	140.748	46.449	1.00	43.53	A	O
ATOM	208	N	TYR	A	34	49.612	141.218	46.184	1.00	40.10	A	N
ATOM	209	CA	TYR	A	34	49.508	141.568	44.769	1.00	39.26	A	C
ATOM	210	CB	TYR	A	34	50.390	142.779	44.450	1.00	36.04	A	C
ATOM	211	CG	TYR	A	34	49.755	144.119	44.736	1.00	34.38	A	C
ATOM	212	CD1	TYR	A	34	49.147	144.854	43.719	1.00	32.49	A	C
ATOM	213	CE1	TYR	A	34	48.566	146.091	43.974	1.00	31.36	A	C
ATOM	214	CD2	TYR	A	34	49.762	144.657	46.024	1.00	35.61	A	C
ATOM	215	CE2	TYR	A	34	49.176	145.894	46.291	1.00	34.99	A	C
ATOM	216	CZ	TYR	A	34	48.580	146.604	45.262	1.00	33.61	A	C
ATOM	217	OH	TYR	A	34	47.972	147.814	45.528	1.00	35.65	A	O
ATOM	218	C	TYR	A	34	49.944	140.385	43.903	1.00	38.44	A	C
ATOM	219	O	TYR	A	34	50.134	140.511	42.694	1.00	42.38	A	O
ATOM	220	N	GLN	A	35	50.109	139.239	44.537	1.00	37.36	A	N
ATOM	221	CA	GLN	A	35	50.506	138.016	43.858	1.00	39.07	A	C
ATOM	222	CB	GLN	A	35	49.407	137.567	42.886	1.00	39.20	A	C
ATOM	223	CG	GLN	A	35	48.093	137.259	43.582	1.00	42.54	A	C
ATOM	224	CD	GLN	A	35	48.253	136.218	44.676	1.00	44.20	A	C
ATOM	225	OE1	GLN	A	35	48.510	135.050	44.399	1.00	46.52	A	O
ATOM	226	NE2	GLN	A	35	48.116	136.643	45.928	1.00	47.31	A	N
ATOM	227	C	GLN	A	35	51.845	138.044	43.137	1.00	38.69	A	C
ATOM	228	O	GLN	A	35	52.015	137.370	42.125	1.00	40.50	A	O
ATOM	229	N	TYR	A	36	52.796	138.811	43.650	1.00	38.35	A	N
ATOM	230	CA	TYR	A	36	54.125	138.854	43.054	1.00	36.94	A	C
ATOM	231	CB	TYR	A	36	54.692	140.260	43.119	1.00	34.85	A	C
ATOM	232	CG	TYR	A	36	54.134	141.156	42.053	1.00	34.00	A	C
ATOM	233	CD1	TYR	A	36	54.886	141.477	40.915	1.00	30.17	A	C
ATOM	234	CE1	TYR	A	36	54.344	142.276	39.902	1.00	30.91	A	C
ATOM	235	CD2	TYR	A	36	52.838	141.653	42.153	1.00	33.30	A	C
ATOM	236	CE2	TYR	A	36	52.292	142.439	41.153	1.00	32.98	A	C
ATOM	237	CZ	TYR	A	36	53.045	142.743	40.030	1.00	32.10	A	C
ATOM	238	OH	TYR	A	36	52.465	143.472	39.019	1.00	35.58	A	O
ATOM	239	C	TYR	A	36	54.983	137.906	43.855	1.00	37.81	A	C
ATOM	240	O	TYR	A	36	55.028	137.999	45.072	1.00	41.95	A	O
ATOM	241	N	GLN	A	37	55.655	136.979	43.187	1.00	39.64	A	N

FIGURE 11-14

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ATOM	242	CA	GLN	A	37	56.477	136.016	43.901	1.00	40.67	A	C
ATOM	243	CB	GLN	A	37	56.062	134.598	43.511	1.00	43.20	A	C
ATOM	244	CG	GLN	A	37	54.736	134.164	44.147	1.00	48.28	A	C
ATOM	245	CD	GLN	A	37	54.202	132.866	43.567	1.00	52.76	A	C
ATOM	246	OE1	GLN	A	37	53.603	132.856	42.489	1.00	54.77	A	O
ATOM	247	NE2	GLN	A	37	54.428	131.758	44.274	1.00	54.90	A	N
ATOM	248	C	GLN	A	37	57.982	136.213	43.727	1.00	42.42	A	C
ATOM	249	O	GLN	A	37	58.485	136.543	42.642	1.00	40.29	A	O
ATOM	250	N	GLU	A	38	58.697	136.008	44.825	1.00	42.52	A	N
ATOM	251	CA	GLU	A	38	60.132	136.188	44.831	1.00	42.23	A	C
ATOM	252	CB	GLU	A	38	60.680	136.153	46.260	1.00	39.16	A	C
ATOM	253	CG	GLU	A	38	62.191	136.106	46.288	1.00	41.31	A	C
ATOM	254	CD	GLU	A	38	62.779	136.372	47.653	1.00	43.49	A	C
ATOM	255	OE1	GLU	A	38	62.124	136.044	48.667	1.00	44.17	A	O
ATOM	256	OE2	GLU	A	38	63.910	136.899	47.708	1.00	42.64	A	O
ATOM	257	C	GLU	A	38	60.912	135.213	43.982	1.00	41.22	A	C
ATOM	258	O	GLU	A	38	60.619	134.029	43.907	1.00	41.31	A	O
ATOM	259	N	ILE	A	39	61.933	135.747	43.344	1.00	41.99	A	N
ATOM	260	CA	ILE	A	39	62.812	134.962	42.514	1.00	42.63	A	C
ATOM	261	CB	ILE	A	39	62.615	135.327	41.054	1.00	43.23	A	C
ATOM	262	CG2	ILE	A	39	62.711	136.833	40.896	1.00	44.67	A	C
ATOM	263	CG1	ILE	A	39	63.634	134.604	40.188	1.00	42.00	A	C
ATOM	264	CD1	ILE	A	39	63.228	134.608	38.752	1.00	47.96	A	C
ATOM	265	C	ILE	A	39	64.195	135.378	42.978	1.00	42.75	A	C
ATOM	266	O	ILE	A	39	64.452	136.572	43.175	1.00	43.83	A	O
ATOM	267	N	ARG	A	40	65.074	134.411	43.196	1.00	40.69	A	N
ATOM	268	CA	ARG	A	40	66.413	134.751	43.648	1.00	41.05	A	C
ATOM	269	CB	ARG	A	40	66.684	134.187	45.041	1.00	38.81	A	C
ATOM	270	CG	ARG	A	40	65.719	134.689	46.080	1.00	41.05	A	C
ATOM	271	CD	ARG	A	40	66.143	134.230	47.450	1.00	40.05	A	C
ATOM	272	NE	ARG	A	40	65.109	134.515	48.434	1.00	39.33	A	N
ATOM	273	CZ	ARG	A	40	65.182	134.162	49.712	1.00	38.94	A	C
ATOM	274	NH1	ARG	A	40	66.248	133.511	50.166	1.00	33.51	A	N
ATOM	275	NH2	ARG	A	40	64.182	134.452	50.535	1.00	39.56	A	N
ATOM	276	C	ARG	A	40	67.479	134.268	42.692	1.00	40.17	A	C
ATOM	277	O	ARG	A	40	67.622	133.074	42.445	1.00	39.69	A	O
ATOM	278	N	THR	A	41	68.229	135.233	42.190	1.00	39.95	A	N
ATOM	279	CA	THR	A	41	69.315	135.036	41.253	1.00	41.63	A	C
ATOM	280	CB	THR	A	41	69.323	136.203	40.274	1.00	40.52	A	C
ATOM	281	OG1	THR	A	41	68.392	135.913	39.225	1.00	43.65	A	O
ATOM	282	CG2	THR	A	41	70.714	136.464	39.716	1.00	46.00	A	C
ATOM	283	C	THR	A	41	70.650	134.946	41.985	1.00	42.73	A	C
ATOM	284	O	THR	A	41	70.802	135.470	43.085	1.00	43.15	A	O
ATOM	285	N	PRO	A	42	71.641	134.275	41.381	1.00	43.47	A	N
ATOM	286	CD	PRO	A	42	71.616	133.478	40.145	1.00	44.24	A	C
ATOM	287	CA	PRO	A	42	72.940	134.160	42.042	1.00	43.71	A	C
ATOM	288	CB	PRO	A	42	73.720	133.242	41.105	1.00	44.91	A	C
ATOM	289	CG	PRO	A	42	72.649	132.430	40.446	1.00	45.17	A	C
ATOM	290	C	PRO	A	42	73.596	135.527	42.181	1.00	42.81	A	C
ATOM	291	O	PRO	A	42	73.252	136.456	41.452	1.00	39.97	A	O
ATOM	292	N	ILE	A	43	74.528	135.643	43.125	1.00	44.34	A	N
ATOM	293	CA	ILE	A	43	75.248	136.893	43.350	1.00	45.56	A	C
ATOM	294	CB	ILE	A	43	76.223	136.779	44.543	1.00	44.47	A	C
ATOM	295	CG2	ILE	A	43	77.221	137.928	44.506	1.00	40.71	A	C
ATOM	296	CG1	ILE	A	43	75.441	136.732	45.865	1.00	43.28	A	C
ATOM	297	CD1	ILE	A	43	74.641	137.987	46.168	1.00	42.18	A	C
ATOM	298	C	ILE	A	43	76.051	137.224	42.097	1.00	48.35	A	C
ATOM	299	O	ILE	A	43	76.280	138.393	41.780	1.00	50.03	A	O
ATOM	300	N	PHE	A	44	76.488	136.189	41.391	1.00	50.81	A	N
ATOM	301	CA	PHE	A	44	77.245	136.405	40.172	1.00	55.25	A	C
ATOM	302	CB	PHE	A	44	78.710	136.006	40.355	1.00	57.11	A	C

FIGURE 11-15

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ATOM	303	CG	PHE	A	44	78.905	134.606	40.831	1.00	60.47	A	C
ATOM	304	CD1	PHE	A	44	78.904	134.316	42.188	1.00	61.19	A	C
ATOM	305	CD2	PHE	A	44	79.109	133.571	39.918	1.00	62.92	A	C
ATOM	306	CE1	PHE	A	44	79.106	133.009	42.638	1.00	64.67	A	C
ATOM	307	CE2	PHE	A	44	79.314	132.254	40.353	1.00	64.03	A	C
ATOM	308	CZ	PHE	A	44	79.314	131.972	41.718	1.00	64.63	A	C
ATOM	309	C	PHE	A	44	76.650	135.664	38.983	1.00	55.67	A	C
ATOM	310	O	PHE	A	44	76.042	134.607	39.138	1.00	56.11	A	O
ATOM	311	N	GLU	A	45	76.823	136.251	37.804	1.00	55.67	A	N
ATOM	312	CA	GLU	A	45	76.327	135.692	36.553	1.00	57.75	A	C
ATOM	313	CB	GLU	A	45	75.301	136.637	35.925	1.00	57.92	A	C
ATOM	314	CG	GLU	A	45	74.015	136.813	36.700	1.00	57.03	A	C
ATOM	315	CD	GLU	A	45	72.916	135.916	36.191	1.00	57.02	A	C
ATOM	316	OE1	GLU	A	45	72.695	135.892	34.964	1.00	58.64	A	O
ATOM	317	OE2	GLU	A	45	72.265	135.245	37.013	1.00	58.63	A	O
ATOM	318	C	GLU	A	45	77.502	135.551	35.591	1.00	59.28	A	C
ATOM	319	O	GLU	A	45	78.580	136.100	35.827	1.00	59.12	A	O
ATOM	320	N	HIS	A	46	77.303	134.819	34.504	1.00	60.92	A	N
ATOM	321	CA	HIS	A	46	78.375	134.686	33.538	1.00	63.15	A	C
ATOM	322	CB	HIS	A	46	78.104	133.523	32.591	1.00	64.78	A	C
ATOM	323	CG	HIS	A	46	78.633	132.218	33.095	1.00	68.09	A	C
ATOM	324	CD2	HIS	A	46	77.999	131.124	33.580	1.00	69.37	A	C
ATOM	325	ND1	HIS	A	46	79.983	131.959	33.206	1.00	70.13	A	N
ATOM	326	CE1	HIS	A	46	80.159	130.764	33.741	1.00	70.50	A	C
ATOM	327	NE2	HIS	A	46	78.971	130.236	33.979	1.00	72.35	A	N
ATOM	328	C	HIS	A	46	78.448	136.007	32.795	1.00	64.28	A	C
ATOM	329	O	HIS	A	46	77.429	136.538	32.360	1.00	64.88	A	O
ATOM	330	N	TYR	A	47	79.661	136.539	32.682	1.00	65.53	A	N
ATOM	331	CA	TYR	A	47	79.923	137.823	32.034	1.00	66.93	A	C
ATOM	332	CB	TYR	A	47	81.375	137.884	31.571	1.00	67.66	A	C
ATOM	333	CG	TYR	A	47	81.789	139.265	31.121	1.00	69.36	A	C
ATOM	334	CD1	TYR	A	47	82.103	140.255	32.055	1.00	69.90	A	C
ATOM	335	CE1	TYR	A	47	82.456	141.546	31.652	1.00	71.18	A	C
ATOM	336	CD2	TYR	A	47	81.840	139.596	29.765	1.00	69.70	A	C
ATOM	337	CE2	TYR	A	47	82.192	140.889	29.349	1.00	71.20	A	C
ATOM	338	CZ	TYR	A	47	82.497	141.857	30.300	1.00	71.39	A	C
ATOM	339	OH	TYR	A	47	82.832	143.134	29.908	1.00	72.13	A	O
ATOM	340	C	TYR	A	47	79.037	138.228	30.857	1.00	67.15	A	C
ATOM	341	O	TYR	A	47	78.430	139.298	30.872	1.00	65.71	A	O
ATOM	342	N	GLU	A	48	78.984	137.381	29.833	1.00	69.31	A	N
ATOM	343	CA	GLU	A	48	78.205	137.672	28.632	1.00	71.99	A	C
ATOM	344	CB	GLU	A	48	78.323	136.509	27.641	1.00	73.56	A	C
ATOM	345	CG	GLU	A	48	79.744	136.338	27.086	1.00	78.25	A	C
ATOM	346	CD	GLU	A	48	79.818	135.393	25.887	1.00	81.71	A	C
ATOM	347	OE1	GLU	A	48	80.930	135.211	25.335	1.00	81.76	A	O
ATOM	348	OE2	GLU	A	48	78.768	134.835	25.493	1.00	83.17	A	O
ATOM	349	C	GLU	A	48	76.737	138.035	28.866	1.00	72.01	A	C
ATOM	350	O	GLU	A	48	76.197	138.905	28.182	1.00	71.81	A	O
ATOM	351	N	VAL	A	49	76.095	137.379	29.827	1.00	72.25	A	N
ATOM	352	CA	VAL	A	49	74.696	137.662	30.144	1.00	72.29	A	C
ATOM	353	CB	VAL	A	49	74.184	136.753	31.293	1.00	72.64	A	C
ATOM	354	CG1	VAL	A	49	72.846	137.268	31.815	1.00	73.26	A	C
ATOM	355	CG2	VAL	A	49	74.043	135.321	30.802	1.00	72.42	A	C
ATOM	356	C	VAL	A	49	74.528	139.118	30.575	1.00	71.91	A	C
ATOM	357	O	VAL	A	49	73.630	139.821	30.113	1.00	72.94	A	O
ATOM	358	N	ILE	A	50	75.404	139.567	31.464	1.00	71.27	A	N
ATOM	359	CA	ILE	A	50	75.346	140.930	31.968	1.00	70.05	A	C
ATOM	360	CB	ILE	A	50	76.160	141.050	33.268	1.00	68.01	A	C
ATOM	361	CG2	ILE	A	50	76.094	142.469	33.803	1.00	67.22	A	C
ATOM	362	CG1	ILE	A	50	75.616	140.053	34.292	1.00	67.41	A	C
ATOM	363	CD1	ILE	A	50	74.105	140.132	34.487	1.00	65.65	A	C

FIGURE 11-16

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ATOM	364	C	ILE	A	50	75.808	141.992	30.966	1.00	70.69	A	C
ATOM	365	O	ILE	A	50	75.226	143.077	30.901	1.00	70.32	A	O
ATOM	366	N	SER	A	51	76.848	141.691	30.191	1.00	70.94	A	N
ATOM	367	CA	SER	A	51	77.331	142.652	29.205	1.00	71.62	A	C
ATOM	368	CB	SER	A	51	78.672	142.202	28.600	1.00	72.28	A	C
ATOM	369	OG	SER	A	51	78.531	141.034	27.810	1.00	72.75	A	O
ATOM	370	C	SER	A	51	76.287	142.817	28.107	1.00	71.03	A	C
ATOM	371	O	SER	A	51	76.063	143.915	27.608	1.00	71.22	A	O
ATOM	372	N	ARG	A	52	75.637	141.719	27.748	1.00	72.03	A	N
ATOM	373	CA	ARG	A	52	74.611	141.745	26.716	1.00	74.35	A	C
ATOM	374	CB	ARG	A	52	74.123	140.315	26.433	1.00	76.53	A	C
ATOM	375	CG	ARG	A	52	73.052	140.181	25.348	1.00	79.09	A	C
ATOM	376	CD	ARG	A	52	73.587	140.533	23.961	1.00	82.08	A	C
ATOM	377	NE	ARG	A	52	72.655	140.160	22.894	1.00	84.03	A	N
ATOM	378	CZ	ARG	A	52	72.312	138.907	22.594	1.00	84.49	A	C
ATOM	379	NH1	ARG	A	52	72.822	137.887	23.277	1.00	84.08	A	N
ATOM	380	NH2	ARG	A	52	71.456	138.671	21.608	1.00	83.77	A	N
ATOM	381	C	ARG	A	52	73.436	142.620	27.154	1.00	74.48	A	C
ATOM	382	O	ARG	A	52	73.031	143.532	26.436	1.00	74.33	A	O
ATOM	383	N	SER	A	53	72.913	142.349	28.348	1.00	75.57	A	N
ATOM	384	CA	SER	A	53	71.765	143.079	28.886	1.00	76.79	A	C
ATOM	385	CB	SER	A	53	71.071	142.237	29.956	1.00	76.20	A	C
ATOM	386	OG	SER	A	53	70.009	142.969	30.543	1.00	75.30	A	O
ATOM	387	C	SER	A	53	72.023	144.470	29.461	1.00	77.50	A	C
ATOM	388	O	SER	A	53	71.367	145.439	29.073	1.00	77.54	A	O
ATOM	389	N	VAL	A	54	72.960	144.565	30.397	1.00	78.44	A	N
ATOM	390	CA	VAL	A	54	73.272	145.843	31.027	1.00	79.41	A	C
ATOM	391	CB	VAL	A	54	73.638	145.639	32.519	1.00	79.37	A	C
ATOM	392	CG1	VAL	A	54	73.733	146.985	33.228	1.00	78.49	A	C
ATOM	393	CG2	VAL	A	54	72.598	144.748	33.188	1.00	77.95	A	C
ATOM	394	C	VAL	A	54	74.412	146.574	30.314	1.00	80.80	A	C
ATOM	395	O	VAL	A	54	74.371	147.797	30.162	1.00	81.00	A	O
ATOM	396	N	GLY	A	55	75.424	145.824	29.878	1.00	82.17	A	N
ATOM	397	CA	GLY	A	55	76.552	146.422	29.178	1.00	83.96	A	C
ATOM	398	C	GLY	A	55	77.905	146.175	29.827	1.00	85.32	A	C
ATOM	399	O	GLY	A	55	78.334	145.033	29.991	1.00	85.15	A	O
ATOM	400	N	ASP	A	56	78.589	147.259	30.178	1.00	86.70	A	N
ATOM	401	CA	ASP	A	56	79.895	147.185	30.830	1.00	87.94	A	C
ATOM	402	CB	ASP	A	56	80.977	146.728	29.838	1.00	88.64	A	C
ATOM	403	CG	ASP	A	56	80.794	147.317	28.451	1.00	89.62	A	C
ATOM	404	OD1	ASP	A	56	80.950	148.547	28.288	1.00	90.29	A	O
ATOM	405	OD2	ASP	A	56	80.491	146.539	27.520	1.00	89.88	A	O
ATOM	406	C	ASP	A	56	80.242	148.545	31.419	1.00	88.11	A	C
ATOM	407	O	ASP	A	56	80.252	148.718	32.639	1.00	88.64	A	O
ATOM	408	N	THR	A	57	80.522	149.507	30.548	1.00	87.83	A	N
ATOM	409	CA	THR	A	57	80.840	150.861	30.978	1.00	87.54	A	C
ATOM	410	CB	THR	A	57	79.542	151.608	31.336	1.00	88.11	A	C
ATOM	411	OG1	THR	A	57	78.759	150.801	32.227	1.00	87.46	A	O
ATOM	412	CG2	THR	A	57	78.729	151.896	30.074	1.00	87.40	A	C
ATOM	413	C	THR	A	57	81.824	150.949	32.155	1.00	86.68	A	C
ATOM	414	O	THR	A	57	82.071	152.039	32.678	1.00	86.82	A	O
ATOM	415	N	THR	A	58	82.376	149.803	32.556	1.00	84.82	A	N
ATOM	416	CA	THR	A	58	83.353	149.701	33.646	1.00	83.71	A	C
ATOM	417	CB	THR	A	58	84.457	150.786	33.520	1.00	84.68	A	C
ATOM	418	OG1	THR	A	58	85.036	150.726	32.210	1.00	86.04	A	O
ATOM	419	CG2	THR	A	58	85.562	150.563	34.555	1.00	84.16	A	C
ATOM	420	C	THR	A	58	82.793	149.750	35.070	1.00	81.92	A	C
ATOM	421	O	THR	A	58	83.497	149.406	36.020	1.00	81.48	A	O
ATOM	422	N	ASP	A	59	81.544	150.175	35.237	1.00	79.50	A	N
ATOM	423	CA	ASP	A	59	80.976	150.224	36.580	1.00	76.99	A	C
ATOM	424	CB	ASP	A	59	79.771	151.177	36.625	1.00	77.44	A	C

FIGURE 11-17

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ATOM	425	CG	ASP	A	59	78.476	150.523	36.162	1.00	78.40	A	C
ATOM	426	OD1	ASP	A	59	78.410	150.047	35.005	1.00	78.78	A	O
ATOM	427	OD2	ASP	A	59	77.518	150.491	36.963	1.00	77.39	A	O
ATOM	428	C	ASP	A	59	80.568	148.809	37.019	1.00	75.26	A	C
ATOM	429	O	ASP	A	59	80.183	148.581	38.168	1.00	74.65	A	O
ATOM	430	N	ILE	A	60	80.686	147.858	36.099	1.00	72.34	A	N
ATOM	431	CA	ILE	A	60	80.326	146.471	36.362	1.00	71.06	A	C
ATOM	432	CB	ILE	A	60	79.751	145.832	35.094	1.00	70.42	A	C
ATOM	433	CG2	ILE	A	60	79.570	144.344	35.289	1.00	68.18	A	C
ATOM	434	CG1	ILE	A	60	78.433	146.521	34.745	1.00	71.01	A	C
ATOM	435	CD1	ILE	A	60	77.867	146.125	33.411	1.00	71.90	A	C
ATOM	436	C	ILE	A	60	81.498	145.630	36.858	1.00	70.98	A	C
ATOM	437	O	ILE	A	60	82.552	145.580	36.221	1.00	71.35	A	O
ATOM	438	N	VAL	A	61	81.304	144.959	37.991	1.00	69.70	A	N
ATOM	439	CA	VAL	A	61	82.349	144.126	38.574	1.00	68.53	A	C
ATOM	440	CB	VAL	A	61	82.144	143.951	40.090	1.00	67.41	A	C
ATOM	441	CG1	VAL	A	61	83.258	143.106	40.673	1.00	65.73	A	C
ATOM	442	CG2	VAL	A	61	82.099	145.313	40.764	1.00	67.41	A	C
ATOM	443	C	VAL	A	61	82.413	142.749	37.933	1.00	69.09	A	C
ATOM	444	O	VAL	A	61	81.494	141.944	38.057	1.00	69.31	A	O
ATOM	445	N	SER	A	62	83.516	142.490	37.244	1.00	71.12	A	N
ATOM	446	CA	SER	A	62	83.732	141.218	36.578	1.00	72.08	A	C
ATOM	447	CB	SER	A	62	83.586	141.390	35.071	1.00	71.44	A	C
ATOM	448	OG	SER	A	62	82.314	141.923	34.758	1.00	70.64	A	O
ATOM	449	C	SER	A	62	85.127	140.705	36.913	1.00	74.11	A	C
ATOM	450	O	SER	A	62	86.009	141.476	37.301	1.00	74.47	A	O
ATOM	451	N	LYS	A	63	85.324	139.403	36.759	1.00	75.47	A	N
ATOM	452	CA	LYS	A	63	86.609	138.797	37.063	1.00	77.45	A	C
ATOM	453	CB	LYS	A	63	86.861	138.841	38.570	1.00	77.68	A	C
ATOM	454	CG	LYS	A	63	85.779	138.153	39.392	1.00	78.23	A	C
ATOM	455	CD	LYS	A	63	86.096	138.202	40.877	1.00	79.79	A	C
ATOM	456	CE	LYS	A	63	85.016	137.526	41.706	1.00	79.00	A	C
ATOM	457	NZ	LYS	A	63	85.336	137.576	43.158	1.00	78.88	A	N
ATOM	458	C	LYS	A	63	86.659	137.353	36.593	1.00	79.07	A	C
ATOM	459	O	LYS	A	63	85.626	136.734	36.333	1.00	79.40	A	O
ATOM	460	N	GLU	A	64	87.875	136.826	36.485	1.00	81.05	A	N
ATOM	461	CA	GLU	A	64	88.091	135.448	36.066	1.00	81.88	A	C
ATOM	462	CB	GLU	A	64	89.430	135.327	35.329	1.00	83.62	A	C
ATOM	463	CG	GLU	A	64	89.543	136.208	34.077	1.00	85.98	A	C
ATOM	464	CD	GLU	A	64	89.155	135.483	32.793	1.00	87.50	A	C
ATOM	465	OE1	GLU	A	64	89.969	134.666	32.305	1.00	88.62	A	O
ATOM	466	OE2	GLU	A	64	88.042	135.724	32.272	1.00	86.64	A	O
ATOM	467	C	GLU	A	64	88.096	134.597	37.333	1.00	81.92	A	C
ATOM	468	O	GLU	A	64	88.973	134.727	38.188	1.00	81.83	A	O
ATOM	469	N	MET	A	65	87.096	133.740	37.460	1.00	81.47	A	N
ATOM	470	CA	MET	A	65	86.984	132.881	38.623	1.00	81.53	A	C
ATOM	471	CB	MET	A	65	85.522	132.809	39.051	1.00	82.79	A	C
ATOM	472	CG	MET	A	65	85.264	132.115	40.365	1.00	84.19	A	C
ATOM	473	SD	MET	A	65	83.486	132.037	40.658	1.00	86.63	A	S
ATOM	474	CE	MET	A	65	83.149	133.750	41.180	1.00	86.12	A	C
ATOM	475	C	MET	A	65	87.499	131.498	38.246	1.00	81.23	A	C
ATOM	476	O	MET	A	65	87.007	130.888	37.295	1.00	80.85	A	O
ATOM	477	N	TYR	A	66	88.496	131.010	38.980	1.00	81.00	A	N
ATOM	478	CA	TYR	A	66	89.062	129.697	38.697	1.00	80.12	A	C
ATOM	479	CB	TYR	A	66	90.277	129.414	39.581	1.00	82.28	A	C
ATOM	480	CG	TYR	A	66	90.733	127.973	39.485	1.00	85.42	A	C
ATOM	481	CD1	TYR	A	66	91.262	127.464	38.296	1.00	86.29	A	C
ATOM	482	CE1	TYR	A	66	91.625	126.121	38.185	1.00	87.19	A	C
ATOM	483	CD2	TYR	A	66	90.582	127.100	40.566	1.00	86.31	A	C
ATOM	484	CE2	TYR	A	66	90.941	125.756	40.466	1.00	86.59	A	C
ATOM	485	CZ	TYR	A	66	91.460	125.273	39.274	1.00	87.37	A	C

FIGURE 11-18

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ATOM	486	OH	TYR	A	66	91.798	123.941	39.167	1.00	87.73	A	O
ATOM	487	C	TYR	A	66	88.043	128.588	38.901	1.00	78.34	A	C
ATOM	488	O	TYR	A	66	87.365	128.533	39.927	1.00	78.10	A	O
ATOM	489	N	ASP	A	67	87.953	127.702	37.914	1.00	76.25	A	N
ATOM	490	CA	ASP	A	67	87.028	126.581	37.954	1.00	75.15	A	C
ATOM	491	CB	ASP	A	67	85.798	126.880	37.095	1.00	74.06	A	C
ATOM	492	CG	ASP	A	67	84.664	125.905	37.337	1.00	74.41	A	C
ATOM	493	OD1	ASP	A	67	84.004	126.008	38.395	1.00	75.25	A	O
ATOM	494	OD2	ASP	A	67	84.434	125.032	36.473	1.00	71.90	A	O
ATOM	495	C	ASP	A	67	87.758	125.360	37.405	1.00	75.27	A	C
ATOM	496	O	ASP	A	67	88.458	125.444	36.399	1.00	75.91	A	O
ATOM	497	N	PHE	A	68	87.594	124.227	38.073	1.00	74.99	A	N
ATOM	498	CA	PHE	A	68	88.244	122.991	37.664	1.00	74.81	A	C
ATOM	499	CB	PHE	A	68	88.240	122.001	38.833	1.00	74.69	A	C
ATOM	500	CG	PHE	A	68	89.002	120.737	38.565	1.00	75.31	A	C
ATOM	501	CD1	PHE	A	68	90.379	120.767	38.363	1.00	76.17	A	C
ATOM	502	CD2	PHE	A	68	88.347	119.512	38.523	1.00	74.46	A	C
ATOM	503	CE1	PHE	A	68	91.094	119.590	38.122	1.00	75.49	A	C
ATOM	504	CE2	PHE	A	68	89.051	118.334	38.282	1.00	75.42	A	C
ATOM	505	CZ	PHE	A	68	90.428	118.373	38.082	1.00	74.43	A	C
ATOM	506	C	PHE	A	68	87.541	122.363	36.464	1.00	74.73	A	C
ATOM	507	O	PHE	A	68	88.153	122.117	35.426	1.00	75.22	A	O
ATOM	508	N	TYR	A	69	86.246	122.120	36.619	1.00	73.94	A	N
ATOM	509	CA	TYR	A	69	85.425	121.492	35.590	1.00	73.78	A	C
ATOM	510	CB	TYR	A	69	84.026	121.307	36.154	1.00	70.56	A	C
ATOM	511	CG	TYR	A	69	84.109	120.760	37.554	1.00	69.36	A	C
ATOM	512	CD1	TYR	A	69	84.763	119.554	37.803	1.00	67.27	A	C
ATOM	513	CE1	TYR	A	69	84.919	119.075	39.090	1.00	65.87	A	C
ATOM	514	CD2	TYR	A	69	83.606	121.475	38.640	1.00	68.09	A	C
ATOM	515	CE2	TYR	A	69	83.757	121.002	39.936	1.00	66.02	A	C
ATOM	516	CZ	TYR	A	69	84.416	119.802	40.151	1.00	65.61	A	C
ATOM	517	OH	TYR	A	69	84.573	119.319	41.423	1.00	62.44	A	O
ATOM	518	C	TYR	A	69	85.390	122.225	34.261	1.00	75.51	A	C
ATOM	519	O	TYR	A	69	85.093	121.635	33.224	1.00	75.60	A	O
ATOM	520	N	ASP	A	70	85.691	123.514	34.297	1.00	78.33	A	N
ATOM	521	CA	ASP	A	70	85.730	124.319	33.088	1.00	81.49	A	C
ATOM	522	CB	ASP	A	70	84.571	125.323	33.078	1.00	82.64	A	C
ATOM	523	CG	ASP	A	70	83.224	124.656	32.798	1.00	84.49	A	C
ATOM	524	OD1	ASP	A	70	83.087	124.010	31.735	1.00	84.97	A	O
ATOM	525	OD2	ASP	A	70	82.301	124.775	33.634	1.00	84.80	A	O
ATOM	526	C	ASP	A	70	87.085	125.021	33.088	1.00	83.11	A	C
ATOM	527	O	ASP	A	70	88.113	124.377	32.861	1.00	82.77	A	O
ATOM	528	N	LYS	A	71	87.092	126.326	33.351	1.00	85.12	A	N
ATOM	529	CA	LYS	A	71	88.334	127.100	33.405	1.00	86.75	A	C
ATOM	530	CB	LYS	A	71	89.261	126.741	32.235	1.00	87.79	A	C
ATOM	531	CG	LYS	A	71	90.678	127.278	32.403	1.00	88.42	A	C
ATOM	532	CD	LYS	A	71	91.267	126.839	33.741	1.00	88.05	A	C
ATOM	533	CE	LYS	A	71	92.597	127.520	34.016	1.00	88.28	A	C
ATOM	534	NZ	LYS	A	71	93.078	127.238	35.396	1.00	87.56	A	N
ATOM	535	C	LYS	A	71	88.081	128.603	33.397	1.00	86.77	A	C
ATOM	536	O	LYS	A	71	88.925	129.382	33.840	1.00	87.22	A	O
ATOM	537	N	ARG	A	74	85.729	130.235	33.954	1.00	67.25	A	N
ATOM	538	CA	ARG	A	74	84.532	130.979	34.328	1.00	67.04	A	C
ATOM	539	CB	ARG	A	74	83.910	130.378	35.597	1.00	67.30	A	C
ATOM	540	CG	ARG	A	74	83.464	128.918	35.444	1.00	70.47	A	C
ATOM	541	CD	ARG	A	74	81.961	128.716	35.677	1.00	72.04	A	C
ATOM	542	NE	ARG	A	74	81.621	128.339	37.053	1.00	73.27	A	N
ATOM	543	CZ	ARG	A	74	81.804	129.110	38.124	1.00	73.04	A	C
ATOM	544	NH1	ARG	A	74	81.461	128.672	39.328	1.00	72.05	A	N
ATOM	545	NH2	ARG	A	74	82.327	130.320	37.998	1.00	73.36	A	N
ATOM	546	C	ARG	A	74	84.820	132.473	34.534	1.00	66.08	A	C

FIGURE 11-19

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ATOM	547	O	ARG	A	74	85.462	132.877	35.506	1.00	65.99	A	O
ATOM	548	N	HIS	A	75	84.347	133.282	33.594	1.00	64.57	A	N
ATOM	549	CA	HIS	A	75	84.510	134.732	33.640	1.00	64.04	A	C
ATOM	550	CB	HIS	A	75	84.831	135.238	32.229	1.00	65.94	A	C
ATOM	551	CG	HIS	A	75	85.016	136.718	32.139	1.00	68.26	A	C
ATOM	552	CD2	HIS	A	75	84.592	137.613	31.216	1.00	69.45	A	C
ATOM	553	ND1	HIS	A	75	85.740	137.438	33.066	1.00	70.20	A	N
ATOM	554	CE1	HIS	A	75	85.751	138.713	32.719	1.00	70.75	A	C
ATOM	555	NE2	HIS	A	75	85.061	138.846	31.600	1.00	69.81	A	N
ATOM	556	C	HIS	A	75	83.170	135.291	34.145	1.00	62.57	A	C
ATOM	557	O	HIS	A	75	82.246	135.521	33.363	1.00	62.59	A	O
ATOM	558	N	VAL	A	76	83.075	135.507	35.455	1.00	60.38	A	N
ATOM	559	CA	VAL	A	76	81.834	135.972	36.068	1.00	59.11	A	C
ATOM	560	CB	VAL	A	76	81.571	135.224	37.390	1.00	58.98	A	C
ATOM	561	CG1	VAL	A	76	81.554	133.729	37.145	1.00	60.37	A	C
ATOM	562	CG2	VAL	A	76	82.634	135.581	38.405	1.00	60.49	A	C
ATOM	563	C	VAL	A	76	81.677	137.462	36.349	1.00	57.65	A	C
ATOM	564	O	VAL	A	76	82.614	138.247	36.238	1.00	58.57	A	O
ATOM	565	N	THR	A	77	80.463	137.828	36.738	1.00	55.09	A	N
ATOM	566	CA	THR	A	77	80.125	139.204	37.044	1.00	52.21	A	C
ATOM	567	CB	THR	A	77	79.439	139.886	35.840	1.00	53.39	A	C
ATOM	568	OG1	THR	A	77	80.309	139.850	34.703	1.00	55.37	A	O
ATOM	569	CG2	THR	A	77	79.093	141.329	36.174	1.00	52.20	A	C
ATOM	570	C	THR	A	77	79.153	139.254	38.214	1.00	49.50	A	C
ATOM	571	O	THR	A	77	78.142	138.542	38.224	1.00	46.95	A	O
ATOM	572	N	LEU	A	78	79.464	140.090	39.201	1.00	47.07	A	N
ATOM	573	CA	LEU	A	78	78.585	140.258	40.358	1.00	44.51	A	C
ATOM	574	CB	LEU	A	78	79.273	141.122	41.411	1.00	44.51	A	C
ATOM	575	CG	LEU	A	78	80.587	140.531	41.930	1.00	45.20	A	C
ATOM	576	CD1	LEU	A	78	81.274	141.530	42.836	1.00	43.61	A	C
ATOM	577	CD2	LEU	A	78	80.310	139.230	42.660	1.00	44.61	A	C
ATOM	578	C	LEU	A	78	77.364	140.972	39.799	1.00	43.14	A	C
ATOM	579	O	LEU	A	78	77.499	141.975	39.088	1.00	42.76	A	O
ATOM	580	N	ARG	A	79	76.170	140.474	40.086	1.00	43.08	A	N
ATOM	581	CA	ARG	A	79	75.001	141.137	39.514	1.00	42.41	A	C
ATOM	582	CB	ARG	A	79	73.702	140.469	39.947	1.00	43.39	A	C
ATOM	583	CG	ARG	A	79	73.389	140.607	41.390	1.00	46.36	A	C
ATOM	584	CD	ARG	A	79	72.073	139.959	41.705	1.00	46.57	A	C
ATOM	585	NE	ARG	A	79	71.819	140.083	43.127	1.00	51.24	A	N
ATOM	586	CZ	ARG	A	79	70.991	139.308	43.803	1.00	51.72	A	C
ATOM	587	NH1	ARG	A	79	70.336	138.344	43.171	1.00	53.45	A	N
ATOM	588	NH2	ARG	A	79	70.824	139.500	45.107	1.00	53.22	A	N
ATOM	589	C	ARG	A	79	74.994	142.609	39.872	1.00	39.98	A	C
ATOM	590	O	ARG	A	79	75.154	142.990	41.028	1.00	39.44	A	O
ATOM	591	N	PRO	A	80	74.855	143.462	38.855	1.00	39.49	A	N
ATOM	592	CD	PRO	A	80	74.965	143.088	37.430	1.00	38.66	A	C
ATOM	593	CA	PRO	A	80	74.832	144.914	39.016	1.00	37.79	A	C
ATOM	594	CB	PRO	A	80	75.444	145.395	37.710	1.00	39.31	A	C
ATOM	595	CG	PRO	A	80	74.850	144.428	36.720	1.00	37.47	A	C
ATOM	596	C	PRO	A	80	73.419	145.450	39.234	1.00	38.95	A	C
ATOM	597	O	PRO	A	80	73.237	146.602	39.631	1.00	38.69	A	O
ATOM	598	N	GLU	A	81	72.429	144.598	38.980	1.00	37.11	A	N
ATOM	599	CA	GLU	A	81	71.026	144.958	39.128	1.00	37.06	A	C
ATOM	600	CB	GLU	A	81	70.581	145.808	37.949	1.00	36.64	A	C
ATOM	601	CG	GLU	A	81	70.767	145.076	36.637	1.00	38.35	A	C
ATOM	602	CD	GLU	A	81	70.056	145.749	35.505	1.00	40.49	A	C
ATOM	603	OE1	GLU	A	81	70.357	146.934	35.261	1.00	43.38	A	O
ATOM	604	OE2	GLU	A	81	69.197	145.094	34.864	1.00	42.92	A	O
ATOM	605	C	GLU	A	81	70.201	143.674	39.150	1.00	35.46	A	C
ATOM	606	O	GLU	A	81	70.723	142.590	38.920	1.00	33.58	A	O
ATOM	607	N	GLY	A	82	68.906	143.807	39.404	1.00	36.72	A	N

FIGURE 11-20

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ATOM	608	CA	GLY	A	82	68.049	142.638	39.467	1.00	37.51	A	C
ATOM	609	C	GLY	A	82	67.321	142.260	38.185	1.00	37.21	A	C
ATOM	610	O	GLY	A	82	67.137	141.075	37.907	1.00	39.76	A	O
ATOM	611	N	THR	A	83	66.929	143.254	37.397	1.00	37.92	A	N
ATOM	612	CA	THR	A	83	66.185	143.020	36.162	1.00	37.68	A	C
ATOM	613	CB	THR	A	83	65.933	144.337	35.444	1.00	36.95	A	C
ATOM	614	OG1	THR	A	83	65.226	145.209	36.331	1.00	35.20	A	O
ATOM	615	CG2	THR	A	83	65.091	144.124	34.200	1.00	37.74	A	C
ATOM	616	C	THR	A	83	66.798	142.023	35.193	1.00	38.32	A	C
ATOM	617	O	THR	A	83	66.233	140.952	34.971	1.00	39.13	A	O
ATOM	618	N	ALA	A	84	67.951	142.366	34.623	1.00	40.89	A	N
ATOM	619	CA	ALA	A	84	68.643	141.484	33.673	1.00	38.99	A	C
ATOM	620	CB	ALA	A	84	70.045	142.024	33.390	1.00	37.18	A	C
ATOM	621	C	ALA	A	84	68.727	140.030	34.154	1.00	38.52	A	C
ATOM	622	O	ALA	A	84	68.318	139.112	33.446	1.00	39.76	A	O
ATOM	623	N	PRO	A	85	69.255	139.803	35.367	1.00	37.87	A	N
ATOM	624	CD	PRO	A	85	69.803	140.782	36.317	1.00	37.28	A	C
ATOM	625	CA	PRO	A	85	69.374	138.446	35.904	1.00	38.12	A	C
ATOM	626	CB	PRO	A	85	69.926	138.675	37.304	1.00	36.56	A	C
ATOM	627	CG	PRO	A	85	70.715	139.927	37.144	1.00	38.37	A	C
ATOM	628	C	PRO	A	85	68.017	137.775	35.950	1.00	40.05	A	C
ATOM	629	O	PRO	A	85	67.896	136.571	35.752	1.00	43.83	A	O
ATOM	630	N	ILE	A	86	66.986	138.556	36.229	1.00	40.14	A	N
ATOM	631	CA	ILE	A	86	65.657	137.992	36.290	1.00	40.04	A	C
ATOM	632	CB	ILE	A	86	64.708	138.938	37.050	1.00	39.41	A	C
ATOM	633	CG2	ILE	A	86	63.256	138.661	36.686	1.00	38.53	A	C
ATOM	634	CG1	ILE	A	86	64.955	138.746	38.551	1.00	39.45	A	C
ATOM	635	CD1	ILE	A	86	64.238	139.711	39.426	1.00	39.24	A	C
ATOM	636	C	ILE	A	86	65.171	137.696	34.883	1.00	38.84	A	C
ATOM	637	O	ILE	A	86	64.426	136.751	34.667	1.00	36.71	A	O
ATOM	638	N	VAL	A	87	65.605	138.497	33.922	1.00	40.62	A	N
ATOM	639	CA	VAL	A	87	65.227	138.251	32.542	1.00	42.66	A	C
ATOM	640	CB	VAL	A	87	65.623	139.430	31.631	1.00	42.87	A	C
ATOM	641	CG1	VAL	A	87	65.293	139.096	30.152	1.00	43.94	A	C
ATOM	642	CG2	VAL	A	87	64.867	140.684	32.070	1.00	41.19	A	C
ATOM	643	C	VAL	A	87	65.947	136.972	32.084	1.00	43.11	A	C
ATOM	644	O	VAL	A	87	65.368	136.134	31.390	1.00	43.67	A	O
ATOM	645	N	ARG	A	88	67.197	136.808	32.506	1.00	43.18	A	N
ATOM	646	CA	ARG	A	88	67.978	135.630	32.132	1.00	43.18	A	C
ATOM	647	CB	ARG	A	88	69.432	135.787	32.613	1.00	42.58	A	C
ATOM	648	CG	ARG	A	88	70.412	134.684	32.176	1.00	40.67	A	C
ATOM	649	CD	ARG	A	88	70.340	133.479	33.096	1.00	40.90	A	C
ATOM	650	NE	ARG	A	88	70.553	133.885	34.482	1.00	43.46	A	N
ATOM	651	CZ	ARG	A	88	70.084	133.233	35.540	1.00	42.32	A	C
ATOM	652	NH1	ARG	A	88	69.372	132.126	35.374	1.00	40.20	A	N
ATOM	653	NH2	ARG	A	88	70.296	133.711	36.763	1.00	41.73	A	N
ATOM	654	C	ARG	A	88	67.327	134.397	32.753	1.00	45.04	A	C
ATOM	655	O	ARG	A	88	67.286	133.329	32.140	1.00	46.21	A	O
ATOM	656	N	ALA	A	89	66.817	134.544	33.973	1.00	43.99	A	N
ATOM	657	CA	ALA	A	89	66.152	133.440	34.653	1.00	42.38	A	C
ATOM	658	CB	ALA	A	89	65.946	133.779	36.120	1.00	43.73	A	C
ATOM	659	C	ALA	A	89	64.804	133.154	33.985	1.00	41.45	A	C
ATOM	660	O	ALA	A	89	64.428	132.003	33.809	1.00	41.84	A	O
ATOM	661	N	PHE	A	90	64.086	134.212	33.619	1.00	41.78	A	N
ATOM	662	CA	PHE	A	90	62.785	134.099	32.955	1.00	41.56	A	C
ATOM	663	CB	PHE	A	90	62.292	135.500	32.572	1.00	38.65	A	C
ATOM	664	CG	PHE	A	90	60.939	135.525	31.910	1.00	36.90	A	C
ATOM	665	CD1	PHE	A	90	59.803	135.122	32.597	1.00	37.70	A	C
ATOM	666	CD2	PHE	A	90	60.795	135.996	30.611	1.00	38.67	A	C
ATOM	667	CE1	PHE	A	90	58.537	135.190	32.005	1.00	33.89	A	C
ATOM	668	CE2	PHE	A	90	59.534	136.067	30.007	1.00	36.35	A	C

FIGURE 11-21

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ATOM	669	CZ	PHE	A	90	58.407	135.664	30.712	1.00	35.92	A	C
ATOM	670	C	PHE	A	90	62.930	133.232	31.689	1.00	43.47	A	C
ATOM	671	O	PHE	A	90	62.259	132.209	31.528	1.00	42.78	A	O
ATOM	672	N	VAL	A	91	63.822	133.661	30.803	1.00	45.03	A	N
ATOM	673	CA	VAL	A	91	64.094	132.974	29.553	1.00	47.00	A	C
ATOM	674	CB	VAL	A	91	65.094	133.787	28.704	1.00	47.50	A	C
ATOM	675	CG1	VAL	A	91	65.420	133.042	27.412	1.00	47.83	A	C
ATOM	676	CG2	VAL	A	91	64.509	135.155	28.399	1.00	44.69	A	C
ATOM	677	C	VAL	A	91	64.651	131.558	29.742	1.00	49.72	A	C
ATOM	678	O	VAL	A	91	64.117	130.595	29.181	1.00	50.05	A	O
ATOM	679	N	GLU	A	92	65.714	131.435	30.534	1.00	49.69	A	N
ATOM	680	CA	GLU	A	92	66.346	130.144	30.772	1.00	51.75	A	C
ATOM	681	CB	GLU	A	92	67.538	130.320	31.718	1.00	55.02	A	C
ATOM	682	CG	GLU	A	92	68.173	129.020	32.194	1.00	60.90	A	C
ATOM	683	CD	GLU	A	92	69.341	129.242	33.159	1.00	64.75	A	C
ATOM	684	OE1	GLU	A	92	69.687	128.299	33.905	1.00	66.65	A	O
ATOM	685	OE2	GLU	A	92	69.919	130.352	33.166	1.00	66.37	A	O
ATOM	686	C	GLU	A	92	65.411	129.050	31.296	1.00	52.12	A	C
ATOM	687	O	GLU	A	92	65.566	127.882	30.933	1.00	53.77	A	O
ATOM	688	N	ASN	A	93	64.445	129.412	32.135	1.00	49.95	A	N
ATOM	689	CA	ASN	A	93	63.509	128.427	32.679	1.00	48.69	A	C
ATOM	690	CB	ASN	A	93	63.259	128.696	34.162	1.00	49.58	A	C
ATOM	691	CG	ASN	A	93	64.523	128.579	34.992	1.00	50.85	A	C
ATOM	692	OD1	ASN	A	93	64.983	127.481	35.284	1.00	50.36	A	O
ATOM	693	ND2	ASN	A	93	65.099	129.716	35.358	1.00	48.96	A	N
ATOM	694	C	ASN	A	93	62.192	128.457	31.923	1.00	49.28	A	C
ATOM	695	O	ASN	A	93	61.206	127.845	32.335	1.00	47.36	A	O
ATOM	696	N	LYS	A	94	62.182	129.179	30.810	1.00	49.65	A	N
ATOM	697	CA	LYS	A	94	60.987	129.275	29.986	1.00	52.68	A	C
ATOM	698	CB	LYS	A	94	60.784	127.963	29.219	1.00	54.58	A	C
ATOM	699	CG	LYS	A	94	61.979	127.580	28.353	1.00	56.15	A	C
ATOM	700	CD	LYS	A	94	61.739	126.292	27.586	1.00	56.76	A	C
ATOM	701	CE	LYS	A	94	62.888	126.010	26.624	1.00	56.17	A	C
ATOM	702	NZ	LYS	A	94	62.681	124.743	25.858	1.00	56.46	A	N
ATOM	703	C	LYS	A	94	59.751	129.585	30.815	1.00	51.96	A	C
ATOM	704	O	LYS	A	94	58.737	128.912	30.705	1.00	53.15	A	O
ATOM	705	N	LEU	A	95	59.838	130.616	31.643	1.00	52.49	A	N
ATOM	706	CA	LEU	A	95	58.717	131.003	32.486	1.00	50.57	A	C
ATOM	707	CB	LEU	A	95	59.220	131.906	33.618	1.00	51.17	A	C
ATOM	708	CG	LEU	A	95	60.309	131.238	34.458	1.00	51.42	A	C
ATOM	709	CD1	LEU	A	95	60.802	132.176	35.544	1.00	50.31	A	C
ATOM	710	CD2	LEU	A	95	59.744	129.957	35.070	1.00	52.72	A	C
ATOM	711	C	LEU	A	95	57.644	131.705	31.652	1.00	50.22	A	C
ATOM	712	O	LEU	A	95	56.584	132.085	32.153	1.00	49.30	A	O
ATOM	713	N	TYR	A	96	57.928	131.885	30.370	1.00	50.26	A	N
ATOM	714	CA	TYR	A	96	56.966	132.510	29.472	1.00	51.56	A	C
ATOM	715	CB	TYR	A	96	57.702	133.176	28.316	1.00	50.88	A	C
ATOM	716	CG	TYR	A	96	58.690	132.256	27.633	1.00	51.47	A	C
ATOM	717	CD1	TYR	A	96	58.269	131.310	26.691	1.00	52.17	A	C
ATOM	718	CE1	TYR	A	96	59.181	130.444	26.079	1.00	51.55	A	C
ATOM	719	CD2	TYR	A	96	60.044	132.312	27.946	1.00	51.61	A	C
ATOM	720	CE2	TYR	A	96	60.960	131.454	27.345	1.00	52.55	A	C
ATOM	721	CZ	TYR	A	96	60.523	130.526	26.411	1.00	52.91	A	C
ATOM	722	OH	TYR	A	96	61.440	129.699	25.806	1.00	54.53	A	O
ATOM	723	C	TYR	A	96	56.055	131.405	28.943	1.00	53.26	A	C
ATOM	724	O	TYR	A	96	55.007	131.672	28.361	1.00	52.62	A	O
ATOM	725	N	GLY	A	97	56.476	130.161	29.166	1.00	55.33	A	N
ATOM	726	CA	GLY	A	97	55.731	129.003	28.706	1.00	58.87	A	C
ATOM	727	C	GLY	A	97	54.255	128.950	29.052	1.00	61.42	A	C
ATOM	728	O	GLY	A	97	53.787	129.685	29.920	1.00	63.37	A	O
ATOM	729	N	PRO	A	98	53.491	128.072	28.381	1.00	62.59	A	N

FIGURE 11-22

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ATOM	730	CD	PRO	A	98	53.934	127.241	27.248	1.00	62.83	A	C
ATOM	731	CA	PRO	A	98	52.051	127.910	28.604	1.00	62.87	A	C
ATOM	732	CB	PRO	A	98	51.659	126.847	27.578	1.00	61.71	A	C
ATOM	733	CG	PRO	A	98	52.653	127.064	26.471	1.00	62.75	A	C
ATOM	734	C	PRO	A	98	51.738	127.462	30.021	1.00	62.46	A	C
ATOM	735	O	PRO	A	98	50.676	127.764	30.561	1.00	61.69	A	O
ATOM	736	N	GLU	A	99	52.675	126.733	30.613	1.00	62.65	A	N
ATOM	737	CA	GLU	A	99	52.509	126.218	31.964	1.00	63.50	A	C
ATOM	738	CB	GLU	A	99	53.689	125.295	32.309	1.00	67.79	A	C
ATOM	739	CG	GLU	A	99	53.579	124.568	33.652	1.00	70.48	A	C
ATOM	740	CD	GLU	A	99	54.934	124.096	34.169	1.00	74.31	A	C
ATOM	741	OE1	GLU	A	99	55.677	123.438	33.398	1.00	73.53	A	O
ATOM	742	OE2	GLU	A	99	55.254	124.388	35.350	1.00	74.17	A	O
ATOM	743	C	GLU	A	99	52.424	127.341	33.000	1.00	62.31	A	C
ATOM	744	O	GLU	A	99	51.862	127.155	34.086	1.00	60.75	A	O
ATOM	745	N	TYR	A	100	52.969	128.508	32.661	1.00	59.71	A	N
ATOM	746	CA	TYR	A	100	52.983	129.613	33.605	1.00	57.19	A	C
ATOM	747	CB	TYR	A	100	54.388	130.205	33.693	1.00	53.48	A	C
ATOM	748	CG	TYR	A	100	55.426	129.181	34.055	1.00	52.74	A	C
ATOM	749	CD1	TYR	A	100	56.173	128.539	33.062	1.00	53.18	A	C
ATOM	750	CE1	TYR	A	100	57.115	127.564	33.385	1.00	52.33	A	C
ATOM	751	CD2	TYR	A	100	55.644	128.821	35.388	1.00	50.62	A	C
ATOM	752	CE2	TYR	A	100	56.584	127.840	35.727	1.00	51.49	A	C
ATOM	753	CZ	TYR	A	100	57.317	127.219	34.719	1.00	53.55	A	C
ATOM	754	OH	TYR	A	100	58.261	126.265	35.039	1.00	56.01	A	O
ATOM	755	C	TYR	A	100	51.987	130.734	33.420	1.00	56.83	A	C
ATOM	756	O	TYR	A	100	51.568	131.067	32.307	1.00	55.46	A	O
ATOM	757	N	THR	A	101	51.630	131.311	34.561	1.00	56.39	A	N
ATOM	758	CA	THR	A	101	50.696	132.420	34.659	1.00	55.80	A	C
ATOM	759	CB	THR	A	101	50.524	132.825	36.142	1.00	57.47	A	C
ATOM	760	OG1	THR	A	101	49.852	134.089	36.228	1.00	59.98	A	O
ATOM	761	CG2	THR	A	101	51.885	132.918	36.825	1.00	57.03	A	C
ATOM	762	C	THR	A	101	51.136	133.649	33.864	1.00	52.79	A	C
ATOM	763	O	THR	A	101	52.322	133.951	33.753	1.00	49.92	A	O
ATOM	764	N	LYS	A	102	50.156	134.345	33.307	1.00	51.37	A	N
ATOM	765	CA	LYS	A	102	50.395	135.552	32.542	1.00	50.10	A	C
ATOM	766	CB	LYS	A	102	49.954	135.379	31.083	1.00	54.57	A	C
ATOM	767	CG	LYS	A	102	51.032	134.942	30.087	1.00	55.76	A	C
ATOM	768	CD	LYS	A	102	51.512	133.519	30.323	1.00	58.52	A	C
ATOM	769	CE	LYS	A	102	52.245	132.970	29.086	1.00	58.16	A	C
ATOM	770	NZ	LYS	A	102	53.140	133.990	28.447	1.00	58.16	A	N
ATOM	771	C	LYS	A	102	49.568	136.667	33.175	1.00	48.26	A	C
ATOM	772	O	LYS	A	102	48.352	136.532	33.338	1.00	47.64	A	O
ATOM	773	N	PRO	A	103	50.221	137.776	33.558	1.00	45.65	A	N
ATOM	774	CD	PRO	A	103	49.575	139.040	33.955	1.00	45.23	A	C
ATOM	775	CA	PRO	A	103	51.668	137.954	33.399	1.00	42.79	A	C
ATOM	776	CB	PRO	A	103	51.829	139.470	33.434	1.00	44.42	A	C
ATOM	777	CG	PRO	A	103	50.758	139.896	34.372	1.00	45.08	A	C
ATOM	778	C	PRO	A	103	52.441	137.250	34.515	1.00	39.29	A	C
ATOM	779	O	PRO	A	103	51.890	136.985	35.579	1.00	38.36	A	O
ATOM	780	N	TYR	A	104	53.697	136.907	34.260	1.00	35.50	A	N
ATOM	781	CA	TYR	A	104	54.506	136.259	35.284	1.00	35.88	A	C
ATOM	782	CB	TYR	A	104	55.719	135.567	34.656	1.00	35.42	A	C
ATOM	783	CG	TYR	A	104	56.417	134.614	35.599	1.00	37.88	A	C
ATOM	784	CD1	TYR	A	104	55.862	133.372	35.908	1.00	39.09	A	C
ATOM	785	CE1	TYR	A	104	56.498	132.496	36.808	1.00	40.87	A	C
ATOM	786	CD2	TYR	A	104	57.622	134.962	36.207	1.00	38.42	A	C
ATOM	787	CE2	TYR	A	104	58.265	134.096	37.104	1.00	38.54	A	C
ATOM	788	CZ	TYR	A	104	57.704	132.870	37.396	1.00	40.90	A	C
ATOM	789	OH	TYR	A	104	58.370	132.003	38.239	1.00	43.38	A	O
ATOM	790	C	TYR	A	104	54.949	137.383	36.227	1.00	36.00	A	C

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ATOM	791	O	TYR A 104	55.760	138.238	35.860	1.00	36.16	A	O
ATOM	792	N	LYS A 105	54.391	137.374	37.435	1.00	36.89	A	N
ATOM	793	CA	LYS A 105	54.645	138.394	38.450	1.00	35.81	A	C
ATOM	794	CB	LYS A 105	53.374	138.650	39.256	1.00	35.04	A	C
ATOM	795	CG	LYS A 105	52.283	139.389	38.502	1.00	35.93	A	C
ATOM	796	CD	LYS A 105	51.077	139.613	39.422	1.00	36.42	A	C
ATOM	797	CE	LYS A 105	50.172	140.692	38.892	1.00	37.80	A	C
ATOM	798	NZ	LYS A 105	49.108	141.009	39.881	1.00	42.68	A	N
ATOM	799	C	LYS A 105	55.762	138.034	39.406	1.00	35.40	A	C
ATOM	800	O	LYS A 105	55.606	137.178	40.271	1.00	35.69	A	O
ATOM	801	N	THR A 106	56.878	138.731	39.286	1.00	36.54	A	N
ATOM	802	CA	THR A 106	58.003	139.425	40.138	1.00	36.40	A	C
ATOM	803	CB	THR A 106	59.075	137.715	39.320	1.00	38.15	A	C
ATOM	804	OG1	THR A 106	60.034	137.132	40.209	1.00	43.31	A	O
ATOM	805	CG2	THR A 106	59.753	138.691	38.380	1.00	36.83	A	C
ATOM	806	C	THR A 106	58.606	139.638	40.839	1.00	34.46	A	C
ATOM	807	O	THR A 106	58.363	140.779	40.465	1.00	34.35	A	O
ATOM	808	N	TYR A 107	59.376	139.385	41.885	1.00	33.98	A	N
ATOM	809	CA	TYR A 107	60.009	140.462	42.617	1.00	33.99	A	C
ATOM	810	CB	TYR A 107	59.078	140.989	43.721	1.00	34.36	A	C
ATOM	811	CG	TYR A 107	59.033	140.188	45.009	1.00	36.34	A	C
ATOM	812	CD1	TYR A 107	60.118	140.185	45.893	1.00	35.87	A	C
ATOM	813	CE1	TYR A 107	60.065	139.490	47.097	1.00	36.55	A	C
ATOM	814	CD2	TYR A 107	57.888	139.465	45.367	1.00	36.87	A	C
ATOM	815	CE2	TYR A 107	57.824	138.762	46.569	1.00	35.62	A	C
ATOM	816	CZ	TYR A 107	58.919	138.781	47.430	1.00	37.27	A	C
ATOM	817	OH	TYR A 107	58.873	138.102	48.630	1.00	40.77	A	O
ATOM	818	C	TYR A 107	61.311	139.953	43.201	1.00	33.89	A	C
ATOM	819	O	TYR A 107	61.479	138.753	43.372	1.00	32.98	A	O
ATOM	820	N	TYR A 108	62.244	140.856	43.474	1.00	33.63	A	N
ATOM	821	CA	TYR A 108	63.512	140.443	44.048	1.00	34.09	A	C
ATOM	822	CB	TYR A 108	64.616	140.377	42.984	1.00	33.78	A	C
ATOM	823	CG	TYR A 108	64.893	141.704	42.345	1.00	36.25	A	C
ATOM	824	CD1	TYR A 108	64.182	142.112	41.217	1.00	36.47	A	C
ATOM	825	CE1	TYR A 108	64.369	143.376	40.668	1.00	37.55	A	C
ATOM	826	CD2	TYR A 108	65.809	142.594	42.912	1.00	32.44	A	C
ATOM	827	CE2	TYR A 108	66.001	143.859	42.375	1.00	35.20	A	C
ATOM	828	CZ	TYR A 108	65.272	144.245	41.254	1.00	37.49	A	C
ATOM	829	OH	TYR A 108	65.403	145.516	40.748	1.00	42.00	A	O
ATOM	830	C	TYR A 108	63.896	141.415	45.154	1.00	33.58	A	C
ATOM	831	O	TYR A 108	63.404	142.540	45.221	1.00	31.68	A	O
ATOM	832	N	MET A 109	64.799	140.974	46.009	1.00	34.48	A	N
ATOM	833	CA	MET A 109	65.213	141.765	47.143	1.00	35.06	A	C
ATOM	834	CB	MET A 109	64.260	141.432	48.274	1.00	38.87	A	C
ATOM	835	CG	MET A 109	64.073	142.445	49.352	1.00	42.71	A	C
ATOM	836	SD	MET A 109	62.765	141.752	50.407	1.00	48.26	A	S
ATOM	837	CE	MET A 109	61.356	142.340	49.570	1.00	41.35	A	C
ATOM	838	C	MET A 109	66.629	141.295	47.469	1.00	36.21	A	C
ATOM	839	O	MET A 109	66.831	140.158	47.882	1.00	33.91	A	O
ATOM	840	N	GLY A 110	67.618	142.152	47.264	1.00	37.08	A	N
ATOM	841	CA	GLY A 110	68.966	141.727	47.556	1.00	34.80	A	C
ATOM	842	C	GLY A 110	70.074	142.666	47.136	1.00	35.78	A	C
ATOM	843	O	GLY A 110	69.855	143.678	46.455	1.00	34.75	A	O
ATOM	844	N	PRO A 111	71.305	142.329	47.532	1.00	34.74	A	N
ATOM	845	CD	PRO A 111	71.680	141.096	48.242	1.00	32.63	A	C
ATOM	846	CA	PRO A 111	72.486	143.124	47.214	1.00	34.82	A	C
ATOM	847	CB	PRO A 111	73.582	142.440	48.027	1.00	34.63	A	C
ATOM	848	CG	PRO A 111	73.172	141.020	47.975	1.00	33.98	A	C
ATOM	849	C	PRO A 111	72.810	143.144	45.722	1.00	35.83	A	C
ATOM	850	O	PRO A 111	72.577	142.173	45.009	1.00	36.25	A	O
ATOM	851	N	MET A 112	73.321	144.280	45.270	1.00	34.53	A	N

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ATOM	852	CA	MET	A	112	73.750	144.461	43.894	1.00	37.54	A	C
ATOM	853	CB	MET	A	112	72.875	145.478	43.161	1.00	37.24	A	C
ATOM	854	CG	MET	A	112	71.432	145.035	42.997	1.00	38.68	A	C
ATOM	855	SD	MET	A	112	71.290	143.433	42.188	1.00	40.03	A	S
ATOM	856	CE	MET	A	112	69.610	142.923	42.633	1.00	32.92	A	C
ATOM	857	C	MET	A	112	75.172	144.995	44.047	1.00	38.95	A	C
ATOM	858	O	MET	A	112	75.546	145.500	45.114	1.00	37.77	A	O
ATOM	859	N	PHE	A	113	75.965	144.879	42.993	1.00	40.21	A	N
ATOM	860	CA	PHE	A	113	77.341	145.321	43.067	1.00	41.56	A	C
ATOM	861	CB	PHE	A	113	78.249	144.094	43.160	1.00	38.41	A	C
ATOM	862	CG	PHE	A	113	77.902	143.183	44.306	1.00	33.77	A	C
ATOM	863	CD1	PHE	A	113	78.480	143.364	45.556	1.00	32.45	A	C
ATOM	864	CD2	PHE	A	113	76.955	142.178	44.146	1.00	31.55	A	C
ATOM	865	CE1	PHE	A	113	78.123	142.560	46.638	1.00	30.29	A	C
ATOM	866	CE2	PHE	A	113	76.588	141.368	45.218	1.00	31.50	A	C
ATOM	867	CZ	PHE	A	113	77.178	141.561	46.474	1.00	31.15	A	C
ATOM	868	C	PHE	A	113	77.711	146.184	41.885	1.00	44.67	A	C
ATOM	869	O	PHE	A	113	77.195	145.998	40.783	1.00	44.98	A	O
ATOM	870	N	ARG	A	114	78.594	147.144	42.141	1.00	48.65	A	N
ATOM	871	CA	ARG	A	114	79.076	148.077	41.133	1.00	52.97	A	C
ATOM	872	CB	ARG	A	114	78.036	149.180	40.874	1.00	54.47	A	C
ATOM	873	CG	ARG	A	114	76.817	148.724	40.049	1.00	58.74	A	C
ATOM	874	CD	ARG	A	114	75.796	149.851	39.844	1.00	60.26	A	C
ATOM	875	NE	ARG	A	114	74.550	149.376	39.233	1.00	62.60	A	N
ATOM	876	CZ	ARG	A	114	73.403	150.058	39.228	1.00	63.41	A	C
ATOM	877	NH1	ARG	A	114	73.332	151.253	39.802	1.00	61.87	A	N
ATOM	878	NH2	ARG	A	114	72.318	149.541	38.657	1.00	63.44	A	N
ATOM	879	C	ARG	A	114	80.381	148.702	41.614	1.00	56.39	A	C
ATOM	880	O	ARG	A	114	80.746	148.582	42.783	1.00	56.08	A	O
ATOM	881	N	TYR	A	115	81.091	149.350	40.697	1.00	61.85	A	N
ATOM	882	CA	TYR	A	115	82.349	150.025	41.014	1.00	65.12	A	C
ATOM	883	CB	TYR	A	115	83.418	149.740	39.951	1.00	64.02	A	C
ATOM	884	CG	TYR	A	115	84.125	148.404	40.020	1.00	62.42	A	C
ATOM	885	CD1	TYR	A	115	84.202	147.585	38.891	1.00	61.89	A	C
ATOM	886	CE1	TYR	A	115	84.902	146.379	38.914	1.00	61.95	A	C
ATOM	887	CD2	TYR	A	115	84.767	147.982	41.184	1.00	62.20	A	C
ATOM	888	CE2	TYR	A	115	85.473	146.774	41.218	1.00	62.56	A	C
ATOM	889	CZ	TYR	A	115	85.536	145.980	40.077	1.00	62.46	A	C
ATOM	890	OH	TYR	A	115	86.245	144.799	40.090	1.00	62.21	A	O
ATOM	891	C	TYR	A	115	82.092	151.527	41.005	1.00	69.37	A	C
ATOM	892	O	TYR	A	115	81.068	152.000	40.499	1.00	67.95	A	O
ATOM	893	N	GLU	A	116	83.043	152.272	41.554	1.00	75.47	A	N
ATOM	894	CA	GLU	A	116	82.967	153.728	41.582	1.00	79.71	A	C
ATOM	895	CB	GLU	A	116	83.540	154.244	42.900	1.00	81.77	A	C
ATOM	896	CG	GLU	A	116	82.710	153.825	44.098	1.00	84.64	A	C
ATOM	897	CD	GLU	A	116	81.275	154.307	43.983	1.00	86.90	A	C
ATOM	898	OE1	GLU	A	116	81.071	155.541	43.929	1.00	87.44	A	O
ATOM	899	OE2	GLU	A	116	80.357	153.457	43.937	1.00	87.20	A	O
ATOM	900	C	GLU	A	116	83.771	154.259	40.390	1.00	81.54	A	C
ATOM	901	O	GLU	A	116	84.557	155.204	40.512	1.00	81.54	A	O
ATOM	902	N	ARG	A	117	83.562	153.623	39.237	1.00	83.80	A	N
ATOM	903	CA	ARG	A	117	84.244	153.978	37.995	1.00	85.76	A	C
ATOM	904	CB	ARG	A	117	85.130	152.816	37.527	1.00	86.12	A	C
ATOM	905	CG	ARG	A	117	86.124	152.314	38.564	1.00	87.37	A	C
ATOM	906	CD	ARG	A	117	86.765	151.011	38.102	1.00	88.50	A	C
ATOM	907	NE	ARG	A	117	87.606	150.400	39.130	1.00	89.21	A	N
ATOM	908	CZ	ARG	A	117	88.045	149.144	39.083	1.00	89.90	A	C
ATOM	909	NH1	ARG	A	117	87.723	148.366	38.058	1.00	89.45	A	N
ATOM	910	NH2	ARG	A	117	88.800	148.659	40.061	1.00	90.29	A	N
ATOM	911	C	ARG	A	117	83.215	154.296	36.909	1.00	86.34	A	C
ATOM	912	O	ARG	A	117	83.040	153.529	35.958	1.00	86.31	A	O

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ATOM	913	N	ARG	A	122	86.378	151.624	43.326	1.00	75.34	A	N
ATOM	914	CA	ARG	A	122	86.172	150.750	44.479	1.00	75.88	A	C
ATOM	915	CB	ARG	A	122	86.217	151.559	45.779	1.00	78.47	A	C
ATOM	916	CG	ARG	A	122	85.969	150.718	47.027	1.00	82.63	A	C
ATOM	917	CD	ARG	A	122	85.946	151.572	48.287	1.00	85.77	A	C
ATOM	918	NE	ARG	A	122	85.644	150.781	49.477	1.00	87.82	A	N
ATOM	919	CZ	ARG	A	122	85.682	151.256	50.719	1.00	89.64	A	C
ATOM	920	NH1	ARG	A	122	86.013	152.523	50.938	1.00	90.31	A	N
ATOM	921	NH2	ARG	A	122	85.384	150.466	51.745	1.00	90.24	A	N
ATOM	922	C	ARG	A	122	84.842	149.992	44.403	1.00	74.09	A	C
ATOM	923	O	ARG	A	122	83.845	150.506	43.876	1.00	74.07	A	O
ATOM	924	N	LEU	A	123	84.839	148.776	44.948	1.00	69.99	A	N
ATOM	925	CA	LEU	A	123	83.661	147.916	44.949	1.00	65.93	A	C
ATOM	926	CB	LEU	A	123	84.071	146.469	45.248	1.00	66.17	A	C
ATOM	927	CG	LEU	A	123	82.932	145.453	45.380	1.00	66.85	A	C
ATOM	928	CD1	LEU	A	123	82.094	145.464	44.115	1.00	66.51	A	C
ATOM	929	CD2	LEU	A	123	83.495	144.064	45.640	1.00	66.88	A	C
ATOM	930	C	LEU	A	123	82.603	148.349	45.957	1.00	62.85	A	C
ATOM	931	O	LEU	A	123	82.893	148.487	47.145	1.00	62.55	A	O
ATOM	932	N	ARG	A	124	81.379	148.560	45.478	1.00	57.65	A	N
ATOM	933	CA	ARG	A	124	80.278	148.953	46.347	1.00	53.23	A	C
ATOM	934	CB	ARG	A	124	79.790	150.363	46.013	1.00	55.67	A	C
ATOM	935	CG	ARG	A	124	80.481	151.447	46.819	1.00	62.01	A	C
ATOM	936	CD	ARG	A	124	79.832	152.796	46.605	1.00	65.84	A	C
ATOM	937	NE	ARG	A	124	78.403	152.773	46.915	1.00	71.69	A	N
ATOM	938	CZ	ARG	A	124	77.603	153.835	46.823	1.00	73.11	A	C
ATOM	939	NH1	ARG	A	124	78.093	155.004	46.428	1.00	72.36	A	N
ATOM	940	NH2	ARG	A	124	76.314	153.733	47.126	1.00	73.01	A	N
ATOM	941	C	ARG	A	124	79.091	147.996	46.314	1.00	48.40	A	C
ATOM	942	O	ARG	A	124	78.638	147.563	45.250	1.00	43.56	A	O
ATOM	943	N	GLN	A	125	78.604	147.672	47.507	1.00	43.67	A	N
ATOM	944	CA	GLN	A	125	77.462	146.798	47.663	1.00	40.10	A	C
ATOM	945	CB	GLN	A	125	77.716	145.756	48.744	1.00	38.76	A	C
ATOM	946	CG	GLN	A	125	76.502	144.877	48.983	1.00	38.55	A	C
ATOM	947	CD	GLN	A	125	76.765	143.742	49.940	1.00	38.37	A	C
ATOM	948	OE1	GLN	A	125	77.858	143.179	49.963	1.00	41.41	A	O
ATOM	949	NE2	GLN	A	125	75.754	143.377	50.720	1.00	36.72	A	N
ATOM	950	C	GLN	A	125	76.263	147.617	48.084	1.00	39.71	A	C
ATOM	951	O	GLN	A	125	76.273	148.189	49.178	1.00	40.48	A	O
ATOM	952	N	PHE	A	126	75.247	147.696	47.222	1.00	37.20	A	N
ATOM	953	CA	PHE	A	126	74.009	148.412	47.563	1.00	34.66	A	C
ATOM	954	CB	PHE	A	126	73.758	149.594	46.623	1.00	33.55	A	C
ATOM	955	CG	PHE	A	126	73.739	149.231	45.161	1.00	34.00	A	C
ATOM	956	CD1	PHE	A	126	74.901	148.795	44.519	1.00	34.95	A	C
ATOM	957	CD2	PHE	A	126	72.577	149.374	44.415	1.00	33.63	A	C
ATOM	958	CE1	PHE	A	126	74.905	148.515	43.157	1.00	35.07	A	C
ATOM	959	CE2	PHE	A	126	72.565	149.095	43.050	1.00	34.69	A	C
ATOM	960	CZ	PHE	A	126	73.731	148.667	42.418	1.00	34.61	A	C
ATOM	961	C	PHE	A	126	72.833	147.429	47.518	1.00	34.00	A	C
ATOM	962	O	PHE	A	126	72.968	146.317	47.019	1.00	33.58	A	O
ATOM	963	N	HIS	A	127	71.676	147.830	48.029	1.00	33.74	A	N
ATOM	964	CA	HIS	A	127	70.548	146.912	48.046	1.00	31.63	A	C
ATOM	965	CB	HIS	A	127	70.262	146.524	49.501	1.00	29.34	A	C
ATOM	966	CG	HIS	A	127	71.474	145.983	50.200	1.00	28.86	A	C
ATOM	967	CD2	HIS	A	127	71.867	144.710	50.450	1.00	26.68	A	C
ATOM	968	ND1	HIS	A	127	72.513	146.791	50.619	1.00	32.19	A	N
ATOM	969	CE1	HIS	A	127	73.493	146.039	51.095	1.00	27.16	A	C
ATOM	970	NE2	HIS	A	127	73.126	144.773	51.003	1.00	28.11	A	N
ATOM	971	C	HIS	A	127	69.309	147.404	47.321	1.00	30.31	A	C
ATOM	972	O	HIS	A	127	68.937	148.568	47.397	1.00	29.09	A	O
ATOM	973	N	GLN	A	128	68.680	146.492	46.596	1.00	32.38	A	N

FIGURE 11-26

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ATOM	974	CA	GLN	A	128	67.512	146.844	45.816	1.00	34.17	A	C
ATOM	975	CB	GLN	A	128	67.855	146.845	44.319	1.00	35.77	A	C
ATOM	976	CG	GLN	A	128	69.058	147.707	43.913	1.00	42.46	A	C
ATOM	977	CD	GLN	A	128	68.806	149.214	44.018	1.00	44.42	A	C
ATOM	978	OE1	GLN	A	128	69.498	149.919	44.753	1.00	50.60	A	O
ATOM	979	NE2	GLN	A	128	67.822	149.708	43.277	1.00	45.38	A	N
ATOM	980	C	GLN	A	128	66.341	145.906	46.035	1.00	33.81	A	C
ATOM	981	O	GLN	A	128	66.483	144.759	46.445	1.00	31.43	A	O
ATOM	982	N	ILE	A	129	65.174	146.443	45.756	1.00	33.31	A	N
ATOM	983	CA	ILE	A	129	63.934	145.716	45.834	1.00	34.68	A	C
ATOM	984	CB	ILE	A	129	63.045	146.225	46.991	1.00	34.84	A	C
ATOM	985	CG2	ILE	A	129	61.619	145.733	46.809	1.00	34.24	A	C
ATOM	986	CG1	ILE	A	129	63.608	145.750	48.331	1.00	34.02	A	C
ATOM	987	CD1	ILE	A	129	62.804	146.238	49.529	1.00	36.35	A	C
ATOM	988	C	ILE	A	129	63.324	146.117	44.498	1.00	34.58	A	C
ATOM	989	O	ILE	A	129	63.315	147.297	44.151	1.00	34.13	A	O
ATOM	990	N	GLY	A	130	62.849	145.145	43.733	1.00	34.85	A	N
ATOM	991	CA	GLY	A	130	62.252	145.475	42.458	1.00	33.27	A	C
ATOM	992	C	GLY	A	130	61.237	144.449	42.022	1.00	33.17	A	C
ATOM	993	O	GLY	A	130	61.180	143.339	42.556	1.00	33.58	A	O
ATOM	994	N	VAL	A	131	60.410	144.830	41.059	1.00	32.57	A	N
ATOM	995	CA	VAL	A	131	59.432	143.911	40.531	1.00	31.32	A	C
ATOM	996	CB	VAL	A	131	57.981	144.280	40.933	1.00	31.61	A	C
ATOM	997	CG1	VAL	A	131	57.844	144.334	42.458	1.00	34.43	A	C
ATOM	998	CG2	VAL	A	131	57.597	145.586	40.332	1.00	29.74	A	C
ATOM	999	C	VAL	A	131	59.522	143.968	39.025	1.00	31.64	A	C
ATOM	1000	O	VAL	A	131	59.960	144.972	38.467	1.00	28.59	A	O
ATOM	1001	N	GLU	A	132	59.118	142.869	38.392	1.00	30.94	A	N
ATOM	1002	CA	GLU	A	132	59.056	142.744	36.949	1.00	33.89	A	C
ATOM	1003	CB	GLU	A	132	60.305	142.047	36.387	1.00	38.15	A	C
ATOM	1004	CG	GLU	A	132	61.639	142.710	36.736	1.00	40.85	A	C
ATOM	1005	CD	GLU	A	132	61.806	144.075	36.106	1.00	44.28	A	C
ATOM	1006	OE1	GLU	A	132	62.795	144.766	36.427	1.00	45.57	A	O
ATOM	1007	OE2	GLU	A	132	60.950	144.462	35.287	1.00	47.61	A	O
ATOM	1008	C	GLU	A	132	57.821	141.875	36.692	1.00	34.15	A	C
ATOM	1009	O	GLU	A	132	57.648	140.824	37.321	1.00	33.37	A	O
ATOM	1010	N	ALA	A	133	56.947	142.337	35.802	1.00	33.12	A	N
ATOM	1011	CA	ALA	A	133	55.753	141.591	35.431	1.00	34.19	A	C
ATOM	1012	CB	ALA	A	133	54.511	142.426	35.705	1.00	32.63	A	C
ATOM	1013	C	ALA	A	133	55.881	141.281	33.929	1.00	35.34	A	C
ATOM	1014	O	ALA	A	133	55.826	142.189	33.091	1.00	33.13	A	O
ATOM	1015	N	PHE	A	134	56.074	140.011	33.585	1.00	36.95	A	N
ATOM	1016	CA	PHE	A	134	56.230	139.644	32.174	1.00	40.04	A	C
ATOM	1017	CB	PHE	A	134	57.378	138.652	31.980	1.00	37.55	A	C
ATOM	1018	CG	PHE	A	134	58.674	139.064	32.617	1.00	39.02	A	C
ATOM	1019	CD1	PHE	A	134	59.053	138.540	33.849	1.00	37.16	A	C
ATOM	1020	CD2	PHE	A	134	59.550	139.912	31.957	1.00	38.40	A	C
ATOM	1021	CE1	PHE	A	134	60.284	138.846	34.404	1.00	36.94	A	C
ATOM	1022	CE2	PHE	A	134	60.787	140.223	32.509	1.00	39.67	A	C
ATOM	1023	CZ	PHE	A	134	61.152	139.685	33.734	1.00	38.11	A	C
ATOM	1024	C	PHE	A	134	55.012	139.028	31.495	1.00	41.89	A	C
ATOM	1025	O	PHE	A	134	54.339	138.163	32.059	1.00	42.17	A	O
ATOM	1026	N	GLY	A	135	54.742	139.471	30.271	1.00	43.96	A	N
ATOM	1027	CA	GLY	A	135	53.652	138.883	29.515	1.00	44.79	A	C
ATOM	1028	C	GLY	A	135	52.457	139.705	29.092	1.00	45.17	A	C
ATOM	1029	O	GLY	A	135	51.842	139.405	28.068	1.00	46.97	A	O
ATOM	1030	N	SER	A	136	52.118	140.737	29.855	1.00	45.10	A	N
ATOM	1031	CA	SER	A	136	50.950	141.531	29.528	1.00	44.06	A	C
ATOM	1032	CB	SER	A	136	50.039	141.610	30.746	1.00	42.31	A	C
ATOM	1033	OG	SER	A	136	48.907	142.410	30.462	1.00	48.56	A	O
ATOM	1034	C	SER	A	136	51.212	142.928	28.991	1.00	45.13	A	C

FIGURE 11-27

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ATOM	1035	O	SER	A	136	52.160	143.603	29.395	1.00	47.84	A	O
ATOM	1036	N	GLU	A	137	50.347	143.359	28.080	1.00	45.54	A	N
ATOM	1037	CA	GLU	A	137	50.451	144.678	27.466	1.00	46.12	A	C
ATOM	1038	CB	GLU	A	137	50.255	144.553	25.950	1.00	47.65	A	C
ATOM	1039	CG	GLU	A	137	51.045	145.575	25.157	1.00	55.87	A	C
ATOM	1040	CD	GLU	A	137	51.225	145.201	23.694	1.00	58.48	A	C
ATOM	1041	OE1	GLU	A	137	51.920	145.964	22.983	1.00	63.18	A	O
ATOM	1042	OE2	GLU	A	137	50.683	144.161	23.254	1.00	58.75	A	O
ATOM	1043	C	GLU	A	137	49.387	145.609	28.056	1.00	43.87	A	C
ATOM	1044	O	GLU	A	137	49.378	146.814	27.795	1.00	42.99	A	O
ATOM	1045	N	ASN	A	138	48.502	145.038	28.868	1.00	41.00	A	N
ATOM	1046	CA	ASN	A	138	47.417	145.795	29.483	1.00	40.19	A	C
ATOM	1047	CB	ASN	A	138	46.579	144.857	30.348	1.00	38.17	A	C
ATOM	1048	CG	ASN	A	138	45.250	145.464	30.737	1.00	40.19	A	C
ATOM	1049	OD1	ASN	A	138	45.095	146.688	30.732	1.00	39.25	A	O
ATOM	1050	ND2	ASN	A	138	44.278	144.610	31.090	1.00	40.53	A	N
ATOM	1051	C	ASN	A	138	47.888	147.006	30.315	1.00	39.67	A	C
ATOM	1052	O	ASN	A	138	48.743	146.882	31.198	1.00	40.46	A	O
ATOM	1053	N	PRO	A	139	47.330	148.196	30.045	1.00	38.48	A	N
ATOM	1054	CD	PRO	A	139	46.321	148.519	29.028	1.00	36.31	A	C
ATOM	1055	CA	PRO	A	139	47.724	149.400	30.792	1.00	38.18	A	C
ATOM	1056	CB	PRO	A	139	46.991	150.528	30.062	1.00	37.30	A	C
ATOM	1057	CG	PRO	A	139	46.656	149.941	28.729	1.00	39.86	A	C
ATOM	1058	C	PRO	A	139	47.267	149.287	32.250	1.00	39.08	A	C
ATOM	1059	O	PRO	A	139	47.761	149.989	33.139	1.00	36.37	A	O
ATOM	1060	N	ALA	A	140	46.308	148.396	32.473	1.00	38.86	A	N
ATOM	1061	CA	ALA	A	140	45.770	148.173	33.799	1.00	39.85	A	C
ATOM	1062	CB	ALA	A	140	44.584	147.207	33.728	1.00	39.90	A	C
ATOM	1063	C	ALA	A	140	46.870	147.608	34.691	1.00	39.76	A	C
ATOM	1064	O	ALA	A	140	46.866	147.829	35.895	1.00	40.22	A	O
ATOM	1065	N	LEU	A	141	47.811	146.874	34.099	1.00	39.83	A	N
ATOM	1066	CA	LEU	A	141	48.912	146.304	34.870	1.00	38.77	A	C
ATOM	1067	CB	LEU	A	141	49.657	145.254	34.041	1.00	39.21	A	C
ATOM	1068	CG	LEU	A	141	50.757	144.450	34.744	1.00	38.42	A	C
ATOM	1069	CD1	LEU	A	141	50.180	143.704	35.930	1.00	37.06	A	C
ATOM	1070	CD2	LEU	A	141	51.389	143.480	33.767	1.00	38.22	A	C
ATOM	1071	C	LEU	A	141	49.859	147.436	35.274	1.00	39.11	A	C
ATOM	1072	O	LEU	A	141	50.358	147.464	36.403	1.00	38.85	A	O
ATOM	1073	N	ASP	A	142	50.090	148.375	34.356	1.00	37.13	A	N
ATOM	1074	CA	ASP	A	142	50.957	149.513	34.640	1.00	37.04	A	C
ATOM	1075	CB	ASP	A	142	50.915	150.574	33.524	1.00	36.91	A	C
ATOM	1076	CG	ASP	A	142	51.288	150.029	32.153	1.00	37.76	A	C
ATOM	1077	OD1	ASP	A	142	51.741	150.827	31.313	1.00	38.85	A	O
ATOM	1078	OD2	ASP	A	142	51.117	148.825	31.894	1.00	40.61	A	O
ATOM	1079	C	ASP	A	142	50.450	150.179	35.912	1.00	36.79	A	C
ATOM	1080	O	ASP	A	142	51.207	150.413	36.851	1.00	35.81	A	O
ATOM	1081	N	VAL	A	143	49.160	150.494	35.928	1.00	35.33	A	N
ATOM	1082	CA	VAL	A	143	48.570	151.159	37.070	1.00	35.89	A	C
ATOM	1083	CB	VAL	A	143	47.141	151.589	36.760	1.00	36.79	A	C
ATOM	1084	CG1	VAL	A	143	46.466	152.158	38.002	1.00	32.20	A	C
ATOM	1085	CG2	VAL	A	143	47.174	152.622	35.655	1.00	34.00	A	C
ATOM	1086	C	VAL	A	143	48.597	150.315	38.324	1.00	37.02	A	C
ATOM	1087	O	VAL	A	143	48.774	150.841	39.423	1.00	38.33	A	O
ATOM	1088	N	GLU	A	144	48.434	149.006	38.176	1.00	37.36	A	N
ATOM	1089	CA	GLU	A	144	48.463	148.141	39.341	1.00	35.80	A	C
ATOM	1090	CB	GLU	A	144	48.190	146.684	38.969	1.00	36.54	A	C
ATOM	1091	CG	GLU	A	144	48.102	145.791	40.210	1.00	38.18	A	C
ATOM	1092	CD	GLU	A	144	48.320	144.316	39.929	1.00	39.75	A	C
ATOM	1093	OE1	GLU	A	144	49.460	143.926	39.576	1.00	39.81	A	O
ATOM	1094	OE2	GLU	A	144	47.348	143.544	40.077	1.00	39.78	A	O
ATOM	1095	C	GLU	A	144	49.843	148.212	39.991	1.00	36.75	A	C

FIGURE 11-28

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ATOM	1096	O	GLU	A	144	49.967	148.331	41.217	1.00	35.32	A	O
ATOM	1097	N	ILE	A	145	50.882	148.131	39.162	1.00	32.89	A	N
ATOM	1098	CA	ILE	A	145	52.229	148.150	39.685	1.00	32.81	A	C
ATOM	1099	CB	ILE	A	145	53.236	147.784	38.597	1.00	30.91	A	C
ATOM	1100	CG2	ILE	A	145	54.648	148.063	39.091	1.00	28.19	A	C
ATOM	1101	CG1	ILE	A	145	53.047	146.307	38.226	1.00	30.41	A	C
ATOM	1102	CD1	ILE	A	145	53.751	145.865	36.959	1.00	27.11	A	C
ATOM	1103	C	ILE	A	145	52.627	149.460	40.355	1.00	33.93	A	C
ATOM	1104	O	ILE	A	145	53.339	149.456	41.376	1.00	34.77	A	O
ATOM	1105	N	MET	A	146	52.167	150.571	39.792	1.00	31.59	A	N
ATOM	1106	CA	MET	A	146	52.467	151.870	40.353	1.00	32.81	A	C
ATOM	1107	CB	MET	A	146	52.070	152.983	39.372	1.00	31.32	A	C
ATOM	1108	CG	MET	A	146	52.903	152.970	38.079	1.00	32.99	A	C
ATOM	1109	SD	MET	A	146	52.715	154.421	37.013	1.00	33.00	A	S
ATOM	1110	CE	MET	A	146	51.066	154.125	36.278	1.00	31.04	A	C
ATOM	1111	C	MET	A	146	51.715	152.010	41.675	1.00	33.04	A	C
ATOM	1112	O	MET	A	146	52.235	152.572	42.644	1.00	33.23	A	O
ATOM	1113	N	ALA	A	147	50.497	151.480	41.707	1.00	32.03	A	N
ATOM	1114	CA	ALA	A	147	49.661	151.529	42.907	1.00	32.58	A	C
ATOM	1115	CB	ALA	A	147	48.268	150.972	42.603	1.00	30.91	A	C
ATOM	1116	C	ALA	A	147	50.318	150.700	44.000	1.00	31.25	A	C
ATOM	1117	O	ALA	A	147	50.350	151.080	45.163	1.00	31.85	A	O
ATOM	1118	N	MET	A	148	50.843	149.556	43.601	1.00	30.88	A	N
ATOM	1119	CA	MET	A	148	51.503	148.667	44.520	1.00	29.14	A	C
ATOM	1120	CB	MET	A	148	51.933	147.408	43.776	1.00	28.58	A	C
ATOM	1121	CG	MET	A	148	52.660	146.429	44.623	1.00	26.39	A	C
ATOM	1122	SD	MET	A	148	52.890	144.887	43.803	1.00	33.17	A	S
ATOM	1123	CE	MET	A	148	54.175	145.351	42.561	1.00	22.10	A	C
ATOM	1124	C	MET	A	148	52.708	149.363	45.143	1.00	31.23	A	C
ATOM	1125	O	MET	A	148	52.936	149.254	46.346	1.00	30.34	A	O
ATOM	1126	N	ALA	A	149	53.483	150.068	44.321	1.00	32.20	A	N
ATOM	1127	CA	ALA	A	149	54.655	150.784	44.813	1.00	32.83	A	C
ATOM	1128	CB	ALA	A	149	55.400	151.463	43.653	1.00	31.41	A	C
ATOM	1129	C	ALA	A	149	54.194	151.831	45.824	1.00	32.18	A	C
ATOM	1130	O	ALA	A	149	54.788	151.979	46.889	1.00	32.86	A	O
ATOM	1131	N	LEU	A	150	53.136	152.559	45.491	1.00	30.54	A	N
ATOM	1132	CA	LEU	A	150	52.634	153.572	46.401	1.00	31.42	A	C
ATOM	1133	CB	LEU	A	150	51.502	154.368	45.746	1.00	32.59	A	C
ATOM	1134	CG	LEU	A	150	51.933	155.358	44.667	1.00	30.95	A	C
ATOM	1135	CD1	LEU	A	150	50.699	155.945	44.018	1.00	33.24	A	C
ATOM	1136	CD2	LEU	A	150	52.762	156.458	45.270	1.00	27.68	A	C
ATOM	1137	C	LEU	A	150	52.145	152.931	47.695	1.00	32.11	A	C
ATOM	1138	O	LEU	A	150	52.450	153.407	48.793	1.00	32.52	A	O
ATOM	1139	N	ASP	A	151	51.388	151.851	47.563	1.00	32.49	A	N
ATOM	1140	CA	ASP	A	151	50.878	151.150	48.726	1.00	35.13	A	C
ATOM	1141	CB	ASP	A	151	50.122	149.893	48.302	1.00	36.95	A	C
ATOM	1142	CG	ASP	A	151	49.456	149.198	49.469	1.00	42.10	A	C
ATOM	1143	OD1	ASP	A	151	49.126	149.885	50.465	1.00	42.02	A	O
ATOM	1144	OD2	ASP	A	151	49.245	147.967	49.391	1.00	48.27	A	O
ATOM	1145	C	ASP	A	151	52.047	150.791	49.634	1.00	33.63	A	C
ATOM	1146	O	ASP	A	151	51.990	150.971	50.851	1.00	33.23	A	O
ATOM	1147	N	PHE	A	152	53.116	150.305	49.021	1.00	32.31	A	N
ATOM	1148	CA	PHE	A	152	54.327	149.936	49.738	1.00	30.67	A	C
ATOM	1149	CB	PHE	A	152	55.388	149.493	48.735	1.00	28.32	A	C
ATOM	1150	CG	PHE	A	152	56.761	149.389	49.319	1.00	27.77	A	C
ATOM	1151	CD1	PHE	A	152	57.072	148.379	50.217	1.00	23.66	A	C
ATOM	1152	CD2	PHE	A	152	57.746	150.302	48.973	1.00	26.36	A	C
ATOM	1153	CE1	PHE	A	152	58.350	148.269	50.763	1.00	26.49	A	C
ATOM	1154	CE2	PHE	A	152	59.039	150.196	49.524	1.00	28.84	A	C
ATOM	1155	CZ	PHE	A	152	59.330	149.170	50.419	1.00	24.40	A	C
ATOM	1156	C	PHE	A	152	54.861	151.096	50.588	1.00	30.66	A	C

FIGURE 11-29

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ATOM	1157	O	PHE	A	152	55.152	150.934	51.776	1.00	31.64	A	O
ATOM	1158	N	PHE	A	153	54.996	152.269	49.988	1.00	30.08	A	N
ATOM	1159	CA	PHE	A	153	55.484	153.406	50.739	1.00	32.71	A	C
ATOM	1160	CB	PHE	A	153	55.776	154.588	49.805	1.00	32.98	A	C
ATOM	1161	CG	PHE	A	153	57.046	154.418	49.025	1.00	35.69	A	C
ATOM	1162	CD1	PHE	A	153	57.017	154.171	47.651	1.00	32.99	A	C
ATOM	1163	CD2	PHE	A	153	58.281	154.422	49.683	1.00	37.04	A	C
ATOM	1164	CE1	PHE	A	153	58.192	153.927	46.947	1.00	33.75	A	C
ATOM	1165	CE2	PHE	A	153	59.471	154.177	48.980	1.00	36.45	A	C
ATOM	1166	CZ	PHE	A	153	59.423	153.928	47.610	1.00	36.03	A	C
ATOM	1167	C	PHE	A	153	54.518	153.803	51.851	1.00	33.43	A	C
ATOM	1168	O	PHE	A	153	54.952	154.134	52.954	1.00	32.37	A	O
ATOM	1169	N	LYS	A	154	53.218	153.769	51.558	1.00	32.94	A	N
ATOM	1170	CA	LYS	A	154	52.206	154.094	52.546	1.00	31.38	A	C
ATOM	1171	CB	LYS	A	154	50.808	153.943	51.951	1.00	34.21	A	C
ATOM	1172	CG	LYS	A	154	49.705	153.852	52.992	1.00	34.61	A	C
ATOM	1173	CD	LYS	A	154	48.337	153.650	52.380	1.00	38.25	A	C
ATOM	1174	CE	LYS	A	154	47.290	153.484	53.491	1.00	45.50	A	C
ATOM	1175	NZ	LYS	A	154	45.866	153.503	53.001	1.00	48.22	A	N
ATOM	1176	C	LYS	A	154	52.353	153.134	53.725	1.00	33.69	A	C
ATOM	1177	O	LYS	A	154	52.191	153.518	54.880	1.00	33.00	A	O
ATOM	1178	N	GLN	A	155	52.667	151.879	53.433	1.00	35.21	A	N
ATOM	1179	CA	GLN	A	155	52.836	150.899	54.497	1.00	37.24	A	C
ATOM	1180	CB	GLN	A	155	52.961	149.499	53.909	1.00	38.04	A	C
ATOM	1181	CG	GLN	A	155	51.632	148.932	53.493	1.00	44.85	A	C
ATOM	1182	CD	GLN	A	155	50.666	148.837	54.663	1.00	46.82	A	C
ATOM	1183	OE1	GLN	A	155	50.943	148.152	55.661	1.00	47.10	A	O
ATOM	1184	NE2	GLN	A	155	49.533	149.531	54.556	1.00	44.03	A	N
ATOM	1185	C	GLN	A	155	54.045	151.209	55.375	1.00	36.29	A	C
ATOM	1186	O	GLN	A	155	54.008	150.995	56.577	1.00	34.83	A	O
ATOM	1187	N	LEU	A	156	55.121	151.700	54.771	1.00	34.74	A	N
ATOM	1188	CA	LEU	A	156	56.305	152.055	55.543	1.00	34.06	A	C
ATOM	1189	CB	LEU	A	156	57.484	152.372	54.615	1.00	31.88	A	C
ATOM	1190	CG	LEU	A	156	58.095	151.222	53.821	1.00	31.16	A	C
ATOM	1191	CD1	LEU	A	156	59.167	151.775	52.905	1.00	32.62	A	C
ATOM	1192	CD2	LEU	A	156	58.668	150.173	54.765	1.00	29.85	A	C
ATOM	1193	C	LEU	A	156	56.020	153.293	56.396	1.00	34.46	A	C
ATOM	1194	O	LEU	A	156	56.710	153.550	57.380	1.00	35.82	A	O
ATOM	1195	N	GLY	A	157	55.008	154.067	56.012	1.00	33.47	A	N
ATOM	1196	CA	GLY	A	157	54.704	155.284	56.745	1.00	30.20	A	C
ATOM	1197	C	GLY	A	157	55.289	156.504	56.044	1.00	29.38	A	C
ATOM	1198	O	GLY	A	157	55.316	157.604	56.598	1.00	29.55	A	O
ATOM	1199	N	ILE	A	158	55.793	156.304	54.830	1.00	27.38	A	N
ATOM	1200	CA	ILE	A	158	56.336	157.403	54.048	1.00	26.39	A	C
ATOM	1201	CB	ILE	A	158	57.320	156.895	52.966	1.00	25.42	A	C
ATOM	1202	CG2	ILE	A	158	57.466	157.937	51.857	1.00	22.99	A	C
ATOM	1203	CG1	ILE	A	158	58.674	156.603	53.621	1.00	24.95	A	C
ATOM	1204	CD1	ILE	A	158	59.685	155.883	52.739	1.00	26.67	A	C
ATOM	1205	C	ILE	A	158	55.136	158.089	53.404	1.00	27.66	A	C
ATOM	1206	O	ILE	A	158	54.382	157.472	52.654	1.00	29.05	A	O
ATOM	1207	N	GLN	A	159	54.968	159.375	53.685	1.00	28.74	A	N
ATOM	1208	CA	GLN	A	159	53.816	160.107	53.182	1.00	30.27	A	C
ATOM	1209	CB	GLN	A	159	53.023	160.663	54.362	1.00	28.91	A	C
ATOM	1210	CG	GLN	A	159	52.430	159.623	55.260	1.00	34.53	A	C
ATOM	1211	CD	GLN	A	159	51.793	160.245	56.490	1.00	37.37	A	C
ATOM	1212	OE1	GLN	A	159	52.459	160.458	57.501	1.00	39.94	A	O
ATOM	1213	NE2	GLN	A	159	50.505	160.557	56.401	1.00	36.40	A	N
ATOM	1214	C	GLN	A	159	54.073	161.257	52.240	1.00	30.30	A	C
ATOM	1215	O	GLN	A	159	53.185	161.644	51.481	1.00	29.64	A	O
ATOM	1216	N	GLN	A	160	55.269	161.822	52.314	1.00	31.28	A	N
ATOM	1217	CA	GLN	A	160	55.597	162.978	51.512	1.00	32.31	A	C

FIGURE 11-30

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ATOM	1218	CB	GLN	A	160	56.525	163.875	52.326	1.00	33.53	A	C
ATOM	1219	CG	GLN	A	160	55.986	164.075	53.737	1.00	32.45	A	C
ATOM	1220	CD	GLN	A	160	56.732	165.125	54.529	1.00	33.07	A	C
ATOM	1221	OE1	GLN	A	160	56.122	165.940	55.226	1.00	35.11	A	O
ATOM	1222	NE2	GLN	A	160	58.049	165.110	54.436	1.00	32.01	A	N
ATOM	1223	C	GLN	A	160	56.205	162.573	50.192	1.00	33.14	A	C
ATOM	1224	O	GLN	A	160	57.400	162.765	49.945	1.00	34.05	A	O
ATOM	1225	N	ILE	A	161	55.359	162.007	49.342	1.00	32.33	A	N
ATOM	1226	CA	ILE	A	161	55.792	161.538	48.037	1.00	32.66	A	C
ATOM	1227	CB	ILE	A	161	55.906	160.016	48.007	1.00	32.02	A	C
ATOM	1228	CG2	ILE	A	161	57.135	159.561	48.776	1.00	31.37	A	C
ATOM	1229	CG1	ILE	A	161	54.635	159.402	48.583	1.00	27.90	A	C
ATOM	1230	CD1	ILE	A	161	54.569	157.894	48.449	1.00	27.21	A	C
ATOM	1231	C	ILE	A	161	54.806	161.929	46.961	1.00	33.67	A	C
ATOM	1232	O	ILE	A	161	53.681	162.341	47.249	1.00	35.12	A	O
ATOM	1233	N	LYS	A	162	55.238	161.807	45.716	1.00	33.45	A	N
ATOM	1234	CA	LYS	A	162	54.369	162.104	44.595	1.00	34.46	A	C
ATOM	1235	CB	LYS	A	162	54.499	163.563	44.145	1.00	36.42	A	C
ATOM	1236	CG	LYS	A	162	55.832	163.950	43.509	1.00	40.98	A	C
ATOM	1237	CD	LYS	A	162	55.728	165.346	42.896	1.00	40.55	A	C
ATOM	1238	CE	LYS	A	162	57.052	165.827	42.305	1.00	42.40	A	C
ATOM	1239	NZ	LYS	A	162	56.890	167.165	41.654	1.00	41.41	A	N
ATOM	1240	C	LYS	A	162	54.696	161.172	43.456	1.00	33.57	A	C
ATOM	1241	O	LYS	A	162	55.855	160.808	43.251	1.00	32.42	A	O
ATOM	1242	N	LEU	A	163	53.661	160.753	42.741	1.00	33.53	A	N
ATOM	1243	CA	LEU	A	163	53.849	159.874	41.604	1.00	32.52	A	C
ATOM	1244	CB	LEU	A	163	52.652	158.942	41.459	1.00	32.31	A	C
ATOM	1245	CG	LEU	A	163	52.566	158.140	40.151	1.00	36.33	A	C
ATOM	1246	CD1	LEU	A	163	53.720	157.142	40.020	1.00	32.38	A	C
ATOM	1247	CD2	LEU	A	163	51.229	157.412	40.140	1.00	37.64	A	C
ATOM	1248	C	LEU	A	163	53.985	160.767	40.375	1.00	31.88	A	C
ATOM	1249	O	LEU	A	163	53.175	161.660	40.157	1.00	34.87	A	O
ATOM	1250	N	VAL	A	164	55.033	160.550	39.595	1.00	30.20	A	N
ATOM	1251	CA	VAL	A	164	55.263	161.336	38.396	1.00	30.60	A	C
ATOM	1252	CB	VAL	A	164	56.571	162.169	38.507	1.00	34.19	A	C
ATOM	1253	CG1	VAL	A	164	56.764	163.040	37.245	1.00	32.04	A	C
ATOM	1254	CG2	VAL	A	164	56.501	163.066	39.742	1.00	31.56	A	C
ATOM	1255	C	VAL	A	164	55.340	160.352	37.229	1.00	30.97	A	C
ATOM	1256	O	VAL	A	164	56.089	159.375	37.264	1.00	29.64	A	O
ATOM	1257	N	ILE	A	165	54.532	160.599	36.207	1.00	31.59	A	N
ATOM	1258	CA	ILE	A	165	54.484	159.706	35.065	1.00	34.30	A	C
ATOM	1259	CB	ILE	A	165	53.127	159.032	34.956	1.00	36.33	A	C
ATOM	1260	CG2	ILE	A	165	52.755	158.371	36.283	1.00	35.78	A	C
ATOM	1261	CG1	ILE	A	165	52.083	160.092	34.568	1.00	33.29	A	C
ATOM	1262	CD1	ILE	A	165	50.690	159.562	34.484	1.00	34.28	A	C
ATOM	1263	C	ILE	A	165	54.698	160.440	33.760	1.00	35.50	A	C
ATOM	1264	O	ILE	A	165	54.734	161.665	33.698	1.00	36.61	A	O
ATOM	1265	N	ASN	A	166	54.815	159.658	32.704	1.00	37.34	A	N
ATOM	1266	CA	ASN	A	166	55.009	160.192	31.381	1.00	37.67	A	C
ATOM	1267	CB	ASN	A	166	56.373	160.887	31.295	1.00	36.94	A	C
ATOM	1268	CG	ASN	A	166	56.595	161.581	29.964	1.00	36.96	A	C
ATOM	1269	OD1	ASN	A	166	55.652	162.055	29.331	1.00	34.31	A	O
ATOM	1270	ND2	ASN	A	166	57.852	161.665	29.546	1.00	35.87	A	N
ATOM	1271	C	ASN	A	166	54.953	158.978	30.487	1.00	37.58	A	C
ATOM	1272	O	ASN	A	166	54.814	157.860	30.969	1.00	37.93	A	O
ATOM	1273	N	SER	A	167	55.019	159.191	29.185	1.00	39.30	A	N
ATOM	1274	CA	SER	A	167	55.013	158.065	28.260	1.00	38.39	A	C
ATOM	1275	CB	SER	A	167	53.649	157.899	27.599	1.00	38.99	A	C
ATOM	1276	OG	SER	A	167	53.711	156.868	26.633	1.00	39.29	A	O
ATOM	1277	C	SER	A	167	56.040	158.344	27.194	1.00	37.79	A	C
ATOM	1278	O	SER	A	167	56.216	159.497	26.782	1.00	36.28	A	O

FIGURE 11-31

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ATOM	1279	N	LEU	A	168	56.735	157.297	26.772	1.00	37.62	A	N
ATOM	1280	CA	LEU	A	168	57.732	157.425	25.717	1.00	39.84	A	C
ATOM	1281	CB	LEU	A	168	59.033	156.697	26.097	1.00	35.67	A	C
ATOM	1282	CG	LEU	A	168	59.781	157.193	27.346	1.00	34.08	A	C
ATOM	1283	CD1	LEU	A	168	61.045	156.380	27.540	1.00	33.90	A	C
ATOM	1284	CD2	LEU	A	168	60.117	158.678	27.215	1.00	33.62	A	C
ATOM	1285	C	LEU	A	168	57.114	156.781	24.475	1.00	42.42	A	C
ATOM	1286	O	LEU	A	168	57.754	156.682	23.427	1.00	44.26	A	O
ATOM	1287	N	GLY	A	169	55.864	156.340	24.612	1.00	41.14	A	N
ATOM	1288	CA	GLY	A	169	55.175	155.698	23.510	1.00	42.48	A	C
ATOM	1289	C	GLY	A	169	55.996	154.619	22.830	1.00	44.24	A	C
ATOM	1290	O	GLY	A	169	56.981	154.129	23.381	1.00	43.91	A	O
ATOM	1291	N	ASP	A	170	55.586	154.253	21.621	1.00	46.17	A	N
ATOM	1292	CA	ASP	A	170	56.267	153.225	20.825	1.00	46.45	A	C
ATOM	1293	CB	ASP	A	170	55.245	152.490	19.979	1.00	46.77	A	C
ATOM	1294	CG	ASP	A	170	54.481	153.429	19.075	1.00	45.14	A	C
ATOM	1295	OD1	ASP	A	170	53.476	153.000	18.476	1.00	45.00	A	O
ATOM	1296	OD2	ASP	A	170	54.895	154.605	18.967	1.00	44.44	A	O
ATOM	1297	C	ASP	A	170	57.314	153.835	19.895	1.00	47.01	A	C
ATOM	1298	O	ASP	A	170	57.510	155.050	19.869	1.00	48.40	A	O
ATOM	1299	N	LYS	A	171	57.957	152.980	19.110	1.00	48.99	A	N
ATOM	1300	CA	LYS	A	171	58.999	153.401	18.180	1.00	50.42	A	C
ATOM	1301	CB	LYS	A	171	59.538	152.187	17.427	1.00	52.12	A	C
ATOM	1302	CG	LYS	A	171	60.145	151.140	18.342	1.00	57.59	A	C
ATOM	1303	CD	LYS	A	171	60.545	149.872	17.589	1.00	61.15	A	C
ATOM	1304	CE	LYS	A	171	60.986	148.774	18.555	1.00	63.24	A	C
ATOM	1305	NZ	LYS	A	171	61.007	147.415	17.917	1.00	66.27	A	N
ATOM	1306	C	LYS	A	171	58.537	154.464	17.192	1.00	50.48	A	C
ATOM	1307	O	LYS	A	171	59.235	155.454	16.974	1.00	51.02	A	O
ATOM	1308	N	GLU	A	172	57.370	154.267	16.588	1.00	50.86	A	N
ATOM	1309	CA	GLU	A	172	56.863	155.255	15.643	1.00	51.65	A	C
ATOM	1310	CB	GLU	A	172	55.447	154.898	15.177	1.00	52.10	A	C
ATOM	1311	CG	GLU	A	172	55.001	155.698	13.958	1.00	54.57	A	C
ATOM	1312	CD	GLU	A	172	53.491	155.797	13.812	1.00	56.80	A	C
ATOM	1313	OE1	GLU	A	172	52.795	154.759	13.875	1.00	56.07	A	O
ATOM	1314	OE2	GLU	A	172	52.998	156.930	13.620	1.00	60.34	A	O
ATOM	1315	C	GLU	A	172	56.833	156.606	16.357	1.00	51.82	A	C
ATOM	1316	O	GLU	A	172	57.407	157.591	15.885	1.00	51.40	A	O
ATOM	1317	N	THR	A	173	56.168	156.633	17.509	1.00	51.04	A	N
ATOM	1318	CA	THR	A	173	56.051	157.847	18.305	1.00	50.99	A	C
ATOM	1319	CB	THR	A	173	55.284	157.572	19.627	1.00	51.51	A	C
ATOM	1320	OG1	THR	A	173	54.007	156.996	19.327	1.00	50.92	A	O
ATOM	1321	CG2	THR	A	173	55.071	158.872	20.412	1.00	50.07	A	C
ATOM	1322	C	THR	A	173	57.427	158.419	18.641	1.00	49.04	A	C
ATOM	1323	O	THR	A	173	57.656	159.623	18.532	1.00	48.57	A	O
ATOM	1324	N	ARG	A	174	58.345	157.558	19.057	1.00	49.30	A	N
ATOM	1325	CA	ARG	A	174	59.679	158.027	19.402	1.00	51.87	A	C
ATOM	1326	CB	ARG	A	174	60.561	156.864	19.856	1.00	52.86	A	C
ATOM	1327	CG	ARG	A	174	60.199	156.320	21.220	1.00	57.33	A	C
ATOM	1328	CD	ARG	A	174	60.537	157.289	22.356	1.00	58.58	A	C
ATOM	1329	NE	ARG	A	174	61.645	156.780	23.161	1.00	62.63	A	N
ATOM	1330	CZ	ARG	A	174	62.921	157.057	22.929	1.00	63.19	A	C
ATOM	1331	NH1	ARG	A	174	63.862	156.544	23.705	1.00	63.36	A	N
ATOM	1332	NH2	ARG	A	174	63.253	157.871	21.936	1.00	65.21	A	N
ATOM	1333	C	ARG	A	174	60.328	158.721	18.219	1.00	52.53	A	C
ATOM	1334	O	ARG	A	174	60.758	159.867	18.323	1.00	52.94	A	O
ATOM	1335	N	ALA	A	175	60.384	158.021	17.091	1.00	53.69	A	N
ATOM	1336	CA	ALA	A	175	60.996	158.554	15.880	1.00	53.92	A	C
ATOM	1337	CB	ALA	A	175	60.765	157.596	14.717	1.00	54.66	A	C
ATOM	1338	C	ALA	A	175	60.509	159.954	15.508	1.00	53.43	A	C
ATOM	1339	O	ALA	A	175	61.317	160.871	15.360	1.00	54.44	A	O

FIGURE 11-32

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ATOM	1340	N	THR	A	176	59.199	160.134	15.374	1.00	51.87	A	N
ATOM	1341	CA	THR	A	176	58.694	161.444	14.990	1.00	52.04	A	C
ATOM	1342	CB	THR	A	176	57.186	161.384	14.561	1.00	52.16	A	C
ATOM	1343	OG1	THR	A	176	56.486	162.517	15.085	1.00	53.49	A	O
ATOM	1344	CG2	THR	A	176	56.531	160.107	15.014	1.00	51.86	A	C
ATOM	1345	C	THR	A	176	58.924	162.561	16.011	1.00	53.24	A	C
ATOM	1346	O	THR	A	176	59.376	163.648	15.639	1.00	54.52	A	O
ATOM	1347	N	TYR	A	177	58.640	162.313	17.289	1.00	53.33	A	N
ATOM	1348	CA	TYR	A	177	58.856	163.345	18.301	1.00	51.35	A	C
ATOM	1349	CB	TYR	A	177	58.357	162.889	19.679	1.00	52.46	A	C
ATOM	1350	CG	TYR	A	177	58.803	163.804	20.804	1.00	49.40	A	C
ATOM	1351	CD1	TYR	A	177	59.888	163.470	21.617	1.00	47.60	A	C
ATOM	1352	CE1	TYR	A	177	60.343	164.342	22.607	1.00	45.86	A	C
ATOM	1353	CD2	TYR	A	177	58.180	165.037	21.012	1.00	49.80	A	C
ATOM	1354	CE2	TYR	A	177	58.627	165.914	21.995	1.00	46.66	A	C
ATOM	1355	CZ	TYR	A	177	59.706	165.561	22.788	1.00	47.09	A	C
ATOM	1356	OH	TYR	A	177	60.134	166.431	23.765	1.00	46.11	A	O
ATOM	1357	C	TYR	A	177	60.335	163.695	18.391	1.00	51.57	A	C
ATOM	1358	O	TYR	A	177	60.694	164.820	18.737	1.00	50.54	A	O
ATOM	1359	N	ARG	A	178	61.186	162.723	18.077	1.00	51.08	A	N
ATOM	1360	CA	ARG	A	178	62.630	162.926	18.110	1.00	52.40	A	C
ATOM	1361	CB	ARG	A	178	63.357	161.629	17.754	1.00	53.46	A	C
ATOM	1362	CG	ARG	A	178	64.870	161.762	17.765	1.00	57.58	A	C
ATOM	1363	CD	ARG	A	178	65.554	160.404	17.736	1.00	61.79	A	C
ATOM	1364	NE	ARG	A	178	66.971	160.516	18.071	1.00	66.28	A	N
ATOM	1365	CZ	ARG	A	178	67.711	159.512	18.533	1.00	69.02	A	C
ATOM	1366	NH1	ARG	A	178	67.168	158.309	18.716	1.00	69.30	A	N
ATOM	1367	NH2	ARG	A	178	68.990	159.712	18.831	1.00	69.14	A	N
ATOM	1368	C	ARG	A	178	63.032	164.008	17.117	1.00	52.84	A	C
ATOM	1369	O	ARG	A	178	63.868	164.869	17.406	1.00	51.08	A	O
ATOM	1370	N	GLN	A	179	62.433	163.942	15.936	1.00	53.43	A	N
ATOM	1371	CA	GLN	A	179	62.710	164.901	14.885	1.00	52.97	A	C
ATOM	1372	CB	GLN	A	179	62.054	164.447	13.577	1.00	52.43	A	C
ATOM	1373	CG	GLN	A	179	62.392	165.316	12.393	1.00	51.30	A	C
ATOM	1374	CD	GLN	A	179	63.884	165.470	12.223	1.00	51.23	A	C
ATOM	1375	OE1	GLN	A	179	64.597	164.488	12.032	1.00	51.82	A	O
ATOM	1376	NE2	GLN	A	179	64.369	166.708	12.303	1.00	51.43	A	N
ATOM	1377	C	GLN	A	179	62.161	166.259	15.303	1.00	52.46	A	C
ATOM	1378	O	GLN	A	179	62.828	167.284	15.153	1.00	54.49	A	O
ATOM	1379	N	ALA	A	180	60.948	166.260	15.841	1.00	50.64	A	N
ATOM	1380	CA	ALA	A	180	60.316	167.502	16.270	1.00	50.84	A	C
ATOM	1381	CB	ALA	A	180	58.897	167.227	16.767	1.00	50.91	A	C
ATOM	1382	C	ALA	A	180	61.116	168.226	17.349	1.00	51.61	A	C
ATOM	1383	O	ALA	A	180	61.165	169.457	17.368	1.00	52.56	A	O
ATOM	1384	N	LEU	A	181	61.739	167.467	18.247	1.00	50.92	A	N
ATOM	1385	CA	LEU	A	181	62.524	168.069	19.316	1.00	51.75	A	C
ATOM	1386	CB	LEU	A	181	62.880	167.032	20.388	1.00	49.45	A	C
ATOM	1387	CG	LEU	A	181	63.688	167.623	21.554	1.00	48.43	A	C
ATOM	1388	CD1	LEU	A	181	62.874	168.727	22.187	1.00	47.38	A	C
ATOM	1389	CD2	LEU	A	181	64.031	166.555	22.588	1.00	47.88	A	C
ATOM	1390	C	LEU	A	181	63.802	168.681	18.763	1.00	52.72	A	C
ATOM	1391	O	LEU	A	181	64.233	169.753	19.193	1.00	54.09	A	O
ATOM	1392	N	ILE	A	182	64.413	167.986	17.812	1.00	54.25	A	N
ATOM	1393	CA	ILE	A	182	65.642	168.465	17.195	1.00	54.71	A	C
ATOM	1394	CB	ILE	A	182	66.211	167.417	16.208	1.00	55.92	A	C
ATOM	1395	CG2	ILE	A	182	67.304	168.043	15.343	1.00	56.07	A	C
ATOM	1396	CG1	ILE	A	182	66.748	166.217	16.997	1.00	56.55	A	C
ATOM	1397	CD1	ILE	A	182	67.275	165.078	16.138	1.00	55.80	A	C
ATOM	1398	C	ILE	A	182	65.361	169.766	16.451	1.00	53.56	A	C
ATOM	1399	O	ILE	A	182	66.140	170.712	16.525	1.00	53.27	A	O
ATOM	1400	N	ASP	A	183	64.228	169.820	15.763	1.00	52.40	A	N

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ATOM	1401	CA	ASP	A	183	63.876	171.009	15.009	1.00	52.80	A	C
ATOM	1402	CB	ASP	A	183	62.610	170.770	14.178	1.00	54.03	A	C
ATOM	1403	CG	ASP	A	183	62.800	169.692	13.118	1.00	56.84	A	C
ATOM	1404	OD1	ASP	A	183	63.959	169.416	12.726	1.00	57.64	A	O
ATOM	1405	OD2	ASP	A	183	61.787	169.124	12.662	1.00	60.40	A	O
ATOM	1406	C	ASP	A	183	63.668	172.179	15.943	1.00	52.54	A	C
ATOM	1407	O	ASP	A	183	63.783	173.344	15.543	1.00	53.22	A	O
ATOM	1408	N	TYR	A	184	63.369	171.867	17.198	1.00	51.51	A	N
ATOM	1409	CA	TYR	A	184	63.142	172.903	18.191	1.00	48.41	A	C
ATOM	1410	CB	TYR	A	184	62.227	172.400	19.305	1.00	44.87	A	C
ATOM	1411	CG	TYR	A	184	62.149	173.386	20.443	1.00	41.57	A	C
ATOM	1412	CD1	TYR	A	184	61.368	174.536	20.333	1.00	40.44	A	C
ATOM	1413	CE1	TYR	A	184	61.360	175.498	21.322	1.00	38.24	A	C
ATOM	1414	CD2	TYR	A	184	62.925	173.221	21.590	1.00	38.58	A	C
ATOM	1415	CE2	TYR	A	184	62.931	174.188	22.593	1.00	41.00	A	C
ATOM	1416	CZ	TYR	A	184	62.150	175.323	22.447	1.00	40.73	A	C
ATOM	1417	OH	TYR	A	184	62.195	176.320	23.389	1.00	41.24	A	O
ATOM	1418	C	TYR	A	184	64.439	173.365	18.829	1.00	49.05	A	C
ATOM	1419	O	TYR	A	184	64.641	174.561	19.055	1.00	49.65	A	O
ATOM	1420	N	LEU	A	185	65.309	172.407	19.126	1.00	48.90	A	N
ATOM	1421	CA	LEU	A	185	66.568	172.695	19.792	1.00	50.06	A	C
ATOM	1422	CB	LEU	A	185	67.101	171.417	20.445	1.00	48.21	A	C
ATOM	1423	CG	LEU	A	185	66.230	170.793	21.541	1.00	48.38	A	C
ATOM	1424	CD1	LEU	A	185	66.935	169.571	22.106	1.00	49.26	A	C
ATOM	1425	CD2	LEU	A	185	65.966	171.802	22.643	1.00	47.76	A	C
ATOM	1426	C	LEU	A	185	67.666	173.328	18.939	1.00	52.03	A	C
ATOM	1427	O	LEU	A	185	68.445	174.143	19.441	1.00	50.64	A	O
ATOM	1428	N	GLU	A	186	67.740	172.953	17.663	1.00	52.41	A	N
ATOM	1429	CA	GLU	A	186	68.772	173.495	16.781	1.00	54.08	A	C
ATOM	1430	CB	GLU	A	186	68.587	172.962	15.356	1.00	56.46	A	C
ATOM	1431	CG	GLU	A	186	68.700	171.442	15.279	1.00	59.41	A	C
ATOM	1432	CD	GLU	A	186	68.698	170.911	13.854	1.00	63.02	A	C
ATOM	1433	OE1	GLU	A	186	67.784	171.278	13.080	1.00	64.23	A	O
ATOM	1434	OE2	GLU	A	186	69.608	170.117	13.514	1.00	63.42	A	O
ATOM	1435	C	GLU	A	186	68.847	175.022	16.787	1.00	52.51	A	C
ATOM	1436	O	GLU	A	186	69.925	175.582	16.953	1.00	52.71	A	O
ATOM	1437	N	PRO	A	187	67.704	175.715	16.621	1.00	52.68	A	N
ATOM	1438	CD	PRO	A	187	66.370	175.166	16.313	1.00	51.51	A	C
ATOM	1439	CA	PRO	A	187	67.670	177.185	16.620	1.00	52.06	A	C
ATOM	1440	CB	PRO	A	187	66.188	177.498	16.429	1.00	50.81	A	C
ATOM	1441	CG	PRO	A	187	65.692	176.331	15.651	1.00	51.27	A	C
ATOM	1442	C	PRO	A	187	68.203	177.800	17.923	1.00	53.64	A	C
ATOM	1443	O	PRO	A	187	68.436	179.015	18.001	1.00	53.73	A	O
ATOM	1444	N	HIS	A	188	68.373	176.961	18.944	1.00	52.99	A	N
ATOM	1445	CA	HIS	A	188	68.865	177.405	20.245	1.00	52.32	A	C
ATOM	1446	CB	HIS	A	188	67.809	177.161	21.326	1.00	49.17	A	C
ATOM	1447	CG	HIS	A	188	66.509	177.857	21.081	1.00	47.19	A	C
ATOM	1448	CD2	HIS	A	188	65.315	177.387	20.646	1.00	47.52	A	C
ATOM	1449	ND1	HIS	A	188	66.331	179.205	21.304	1.00	45.21	A	N
ATOM	1450	CE1	HIS	A	188	65.085	179.535	21.020	1.00	46.24	A	C
ATOM	1451	NE2	HIS	A	188	64.446	178.450	20.620	1.00	46.81	A	N
ATOM	1452	C	HIS	A	188	70.123	176.640	20.625	1.00	54.46	A	C
ATOM	1453	O	HIS	A	188	70.649	176.801	21.727	1.00	55.71	A	O
ATOM	1454	N	MET	A	189	70.600	175.801	19.717	1.00	55.99	A	N
ATOM	1455	CA	MET	A	189	71.778	174.991	19.981	1.00	59.25	A	C
ATOM	1456	CB	MET	A	189	72.287	174.386	18.674	1.00	62.05	A	C
ATOM	1457	CG	MET	A	189	73.556	173.559	18.804	1.00	63.37	A	C
ATOM	1458	SD	MET	A	189	73.807	172.476	17.362	1.00	67.91	A	S
ATOM	1459	CE	MET	A	189	72.797	173.324	16.082	1.00	64.89	A	C
ATOM	1460	C	MET	A	189	72.908	175.724	20.690	1.00	61.05	A	C
ATOM	1461	O	MET	A	189	73.450	175.225	21.675	1.00	62.20	A	O

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ATOM	1462	N	ALA	A	190	73.259	176.909	20.205	1.00	62.44	A	N
ATOM	1463	CA	ALA	A	190	74.349	177.671	20.805	1.00	64.54	A	C
ATOM	1464	CB	ALA	A	190	74.566	178.962	20.030	1.00	65.44	A	C
ATOM	1465	C	ALA	A	190	74.150	177.982	22.289	1.00	65.85	A	C
ATOM	1466	O	ALA	A	190	75.119	178.083	23.043	1.00	65.06	A	O
ATOM	1467	N	GLU	A	191	72.899	178.124	22.715	1.00	67.77	A	N
ATOM	1468	CA	GLU	A	191	72.630	178.442	24.112	1.00	68.10	A	C
ATOM	1469	CB	GLU	A	191	71.348	179.271	24.233	1.00	70.80	A	C
ATOM	1470	CG	GLU	A	191	71.513	180.467	25.156	1.00	73.51	A	C
ATOM	1471	CD	GLU	A	191	72.396	181.544	24.548	1.00	75.01	A	C
ATOM	1472	OE1	GLU	A	191	73.146	182.199	25.304	1.00	75.81	A	O
ATOM	1473	OE2	GLU	A	191	72.331	181.742	23.313	1.00	74.87	A	O
ATOM	1474	C	GLU	A	191	72.538	177.216	25.018	1.00	67.23	A	C
ATOM	1475	O	GLU	A	191	72.450	177.350	26.242	1.00	66.99	A	O
ATOM	1476	N	LEU	A	192	72.559	176.025	24.428	1.00	64.91	A	N
ATOM	1477	CA	LEU	A	192	72.492	174.805	25.224	1.00	63.18	A	C
ATOM	1478	CB	LEU	A	192	72.193	173.597	24.338	1.00	58.38	A	C
ATOM	1479	CG	LEU	A	192	70.776	173.537	23.773	1.00	55.72	A	C
ATOM	1480	CD1	LEU	A	192	70.619	172.285	22.933	1.00	55.73	A	C
ATOM	1481	CD2	LEU	A	192	69.761	173.542	24.916	1.00	54.99	A	C
ATOM	1482	C	LEU	A	192	73.798	174.584	25.974	1.00	64.46	A	C
ATOM	1483	O	LEU	A	192	74.862	175.010	25.527	1.00	64.15	A	O
ATOM	1484	N	SER	A	193	73.707	173.919	27.121	1.00	66.04	A	N
ATOM	1485	CA	SER	A	193	74.875	173.633	27.946	1.00	67.12	A	C
ATOM	1486	CB	SER	A	193	74.457	172.869	29.196	1.00	66.76	A	C
ATOM	1487	OG	SER	A	193	74.029	171.564	28.854	1.00	65.80	A	O
ATOM	1488	C	SER	A	193	75.894	172.798	27.184	1.00	68.44	A	C
ATOM	1489	O	SER	A	193	75.621	172.327	26.079	1.00	68.75	A	O
ATOM	1490	N	GLU	A	194	77.066	172.614	27.784	1.00	69.72	A	N
ATOM	1491	CA	GLU	A	194	78.121	171.823	27.168	1.00	72.05	A	C
ATOM	1492	CB	GLU	A	194	79.310	171.652	28.125	1.00	75.45	A	C
ATOM	1493	CG	GLU	A	194	80.474	172.623	27.915	1.00	78.77	A	C
ATOM	1494	CD	GLU	A	194	81.752	172.172	28.630	1.00	81.32	A	C
ATOM	1495	OE1	GLU	A	194	82.778	172.886	28.536	1.00	82.30	A	O
ATOM	1496	OE2	GLU	A	194	81.733	171.102	29.283	1.00	80.61	A	O
ATOM	1497	C	GLU	A	194	77.573	170.451	26.826	1.00	71.74	A	C
ATOM	1498	O	GLU	A	194	77.426	170.094	25.659	1.00	70.79	A	O
ATOM	1499	N	ASP	A	195	77.269	169.683	27.864	1.00	72.77	A	N
ATOM	1500	CA	ASP	A	195	76.745	168.343	27.682	1.00	73.51	A	C
ATOM	1501	CB	ASP	A	195	76.357	167.751	29.035	1.00	76.66	A	C
ATOM	1502	CG	ASP	A	195	77.066	166.444	29.316	1.00	79.14	A	C
ATOM	1503	OD1	ASP	A	195	76.947	165.517	28.482	1.00	80.54	A	O
ATOM	1504	OD2	ASP	A	195	77.741	166.343	30.365	1.00	79.76	A	O
ATOM	1505	C	ASP	A	195	75.545	168.318	26.741	1.00	72.26	A	C
ATOM	1506	O	ASP	A	195	75.526	167.558	25.771	1.00	71.25	A	O
ATOM	1507	N	SER	A	196	74.551	169.156	27.027	1.00	70.82	A	N
ATOM	1508	CA	SER	A	196	73.344	169.221	26.209	1.00	70.41	A	C
ATOM	1509	CB	SER	A	196	72.424	170.335	26.710	1.00	70.66	A	C
ATOM	1510	OG	SER	A	196	71.955	170.060	28.019	1.00	70.01	A	O
ATOM	1511	C	SER	A	196	73.611	169.412	24.719	1.00	70.65	A	C
ATOM	1512	O	SER	A	196	72.902	168.851	23.888	1.00	70.46	A	O
ATOM	1513	N	GLN	A	197	74.626	170.200	24.375	1.00	71.88	A	N
ATOM	1514	CA	GLN	A	197	74.956	170.431	22.966	1.00	73.00	A	C
ATOM	1515	CB	GLN	A	197	75.953	171.585	22.821	1.00	72.13	A	C
ATOM	1516	CG	GLN	A	197	75.282	172.943	22.701	1.00	71.86	A	C
ATOM	1517	CD	GLN	A	197	76.269	174.070	22.511	1.00	71.16	A	C
ATOM	1518	OE1	GLN	A	197	77.036	174.396	23.412	1.00	69.32	A	O
ATOM	1519	NE2	GLN	A	197	76.257	174.672	21.330	1.00	72.65	A	N
ATOM	1520	C	GLN	A	197	75.508	169.197	22.266	1.00	73.69	A	C
ATOM	1521	O	GLN	A	197	75.240	168.977	21.085	1.00	72.86	A	O
ATOM	1522	N	ARG	A	198	76.281	168.395	22.991	1.00	76.26	A	N

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ATOM	1523	CA	ARG	A	198	76.852	167.184	22.416	1.00	78.78	A	C
ATOM	1524	CB	ARG	A	198	77.997	166.657	23.287	1.00	80.50	A	C
ATOM	1525	CG	ARG	A	198	79.161	167.628	23.409	1.00	83.85	A	C
ATOM	1526	CD	ARG	A	198	80.441	166.944	23.868	1.00	85.69	A	C
ATOM	1527	NE	ARG	A	198	81.554	167.891	23.932	1.00	88.37	A	N
ATOM	1528	CZ	ARG	A	198	82.832	167.545	24.073	1.00	89.82	A	C
ATOM	1529	NH1	ARG	A	198	83.171	166.263	24.164	1.00	90.02	A	N
ATOM	1530	NH2	ARG	A	198	83.774	168.482	24.127	1.00	89.71	A	N
ATOM	1531	C	ARG	A	198	75.779	166.118	22.271	1.00	79.26	A	C
ATOM	1532	O	ARG	A	198	75.801	165.328	21.328	1.00	79.99	A	O
ATOM	1533	N	ARG	A	199	74.833	166.110	23.204	1.00	79.41	A	N
ATOM	1534	CA	ARG	A	199	73.750	165.140	23.183	1.00	80.27	A	C
ATOM	1535	CB	ARG	A	199	73.248	164.900	24.614	1.00	80.89	A	C
ATOM	1536	CG	ARG	A	199	74.188	164.018	25.433	1.00	82.79	A	C
ATOM	1537	CD	ARG	A	199	74.482	164.560	26.832	1.00	84.19	A	C
ATOM	1538	NE	ARG	A	199	73.348	164.467	27.751	1.00	86.52	A	N
ATOM	1539	CZ	ARG	A	199	73.448	164.601	29.074	1.00	87.75	A	C
ATOM	1540	NH1	ARG	A	199	74.630	164.832	29.635	1.00	87.92	A	N
ATOM	1541	NH2	ARG	A	199	72.370	164.506	29.844	1.00	87.41	A	N
ATOM	1542	C	ARG	A	199	72.596	165.555	22.270	1.00	80.02	A	C
ATOM	1543	O	ARG	A	199	71.734	164.743	21.945	1.00	80.55	A	O
ATOM	1544	N	LEU	A	200	72.596	166.811	21.834	1.00	79.96	A	N
ATOM	1545	CA	LEU	A	200	71.535	167.321	20.969	1.00	80.20	A	C
ATOM	1546	CB	LEU	A	200	71.897	168.718	20.456	1.00	79.61	A	C
ATOM	1547	CG	LEU	A	200	70.730	169.626	20.049	1.00	79.11	A	C
ATOM	1548	CD1	LEU	A	200	71.248	171.024	19.776	1.00	79.00	A	C
ATOM	1549	CD2	LEU	A	200	70.029	169.071	18.829	1.00	79.06	A	C
ATOM	1550	C	LEU	A	200	71.218	166.398	19.792	1.00	80.88	A	C
ATOM	1551	O	LEU	A	200	70.051	166.200	19.457	1.00	81.14	A	O
ATOM	1552	N	HIS	A	201	72.246	165.840	19.160	1.00	82.35	A	N
ATOM	1553	CA	HIS	A	201	72.040	164.927	18.031	1.00	83.77	A	C
ATOM	1554	CB	HIS	A	201	73.020	165.246	16.894	1.00	85.91	A	C
ATOM	1555	CG	HIS	A	201	72.690	166.506	16.151	1.00	88.68	A	C
ATOM	1556	CD2	HIS	A	201	73.341	167.691	16.071	1.00	89.00	A	C
ATOM	1557	ND1	HIS	A	201	71.547	166.644	15.391	1.00	89.41	A	N
ATOM	1558	CE1	HIS	A	201	71.508	167.860	14.875	1.00	89.37	A	C
ATOM	1559	NE2	HIS	A	201	72.584	168.516	15.272	1.00	89.99	A	N
ATOM	1560	C	HIS	A	201	72.210	163.477	18.483	1.00	83.04	A	C
ATOM	1561	O	HIS	A	201	71.458	162.593	18.063	1.00	82.40	A	O
ATOM	1562	N	GLU	A	202	73.204	163.251	19.339	1.00	82.11	A	N
ATOM	1563	CA	GLU	A	202	73.496	161.933	19.900	1.00	80.69	A	C
ATOM	1564	CB	GLU	A	202	74.394	162.110	21.127	1.00	81.79	A	C
ATOM	1565	CG	GLU	A	202	74.906	160.837	21.761	1.00	84.81	A	C
ATOM	1566	CD	GLU	A	202	75.680	161.113	23.047	1.00	87.19	A	C
ATOM	1567	OE1	GLU	A	202	76.711	161.826	22.991	1.00	87.67	A	O
ATOM	1568	OE2	GLU	A	202	75.253	160.619	24.115	1.00	87.41	A	O
ATOM	1569	C	GLU	A	202	72.166	161.279	20.295	1.00	78.70	A	C
ATOM	1570	O	GLU	A	202	71.876	160.146	19.912	1.00	79.59	A	O
ATOM	1571	N	ASN	A	203	71.368	162.013	21.066	1.00	75.44	A	N
ATOM	1572	CA	ASN	A	203	70.050	161.573	21.511	1.00	72.38	A	C
ATOM	1573	CB	ASN	A	203	70.150	160.345	22.425	1.00	74.28	A	C
ATOM	1574	CG	ASN	A	203	70.987	160.598	23.656	1.00	75.76	A	C
ATOM	1575	OD1	ASN	A	203	72.190	160.844	23.563	1.00	76.47	A	O
ATOM	1576	ND2	ASN	A	203	70.352	160.540	24.825	1.00	76.85	A	N
ATOM	1577	C	ASN	A	203	69.398	162.747	22.241	1.00	68.68	A	C
ATOM	1578	O	ASN	A	203	69.624	162.966	23.430	1.00	68.04	A	O
ATOM	1579	N	PRO	A	204	68.579	163.522	21.516	1.00	65.32	A	N
ATOM	1580	CD	PRO	A	204	68.205	163.167	20.136	1.00	63.99	A	C
ATOM	1581	CA	PRO	A	204	67.837	164.710	21.958	1.00	62.85	A	C
ATOM	1582	CB	PRO	A	204	66.851	164.946	20.815	1.00	63.09	A	C
ATOM	1583	CG	PRO	A	204	67.588	164.444	19.634	1.00	65.10	A	C

FIGURE 11-36

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ATOM	1584	C	PRO	A	204	67.120	164.631	23.299	1.00	59.92	A	C
ATOM	1585	O	PRO	A	204	67.316	165.485	24.158	1.00	56.76	A	O
ATOM	1586	N	LEU	A	205	66.272	163.619	23.457	1.00	59.26	A	N
ATOM	1587	CA	LEU	A	205	65.490	163.436	24.677	1.00	57.62	A	C
ATOM	1588	CB	LEU	A	205	64.930	162.008	24.726	1.00	57.61	A	C
ATOM	1589	CG	LEU	A	205	63.882	161.542	23.706	1.00	56.20	A	C
ATOM	1590	CD1	LEU	A	205	62.547	162.145	24.029	1.00	55.06	A	C
ATOM	1591	CD2	LEU	A	205	64.311	161.913	22.291	1.00	57.88	A	C
ATOM	1592	C	LEU	A	205	66.287	163.734	25.956	1.00	57.72	A	C
ATOM	1593	O	LEU	A	205	65.745	164.281	26.919	1.00	56.26	A	O
ATOM	1594	N	ARG	A	206	67.571	163.385	25.957	1.00	58.21	A	N
ATOM	1595	CA	ARG	A	206	68.437	163.619	27.115	1.00	60.02	A	C
ATOM	1596	CB	ARG	A	206	69.863	163.156	26.801	1.00	62.79	A	C
ATOM	1597	CG	ARG	A	206	70.329	161.930	27.595	1.00	68.46	A	C
ATOM	1598	CD	ARG	A	206	70.684	162.287	29.048	1.00	71.63	A	C
ATOM	1599	NE	ARG	A	206	69.641	161.949	30.020	1.00	75.30	A	N
ATOM	1600	CZ	ARG	A	206	69.313	160.705	30.374	1.00	77.10	A	C
ATOM	1601	NH1	ARG	A	206	69.943	159.667	29.835	1.00	78.10	A	N
ATOM	1602	NH2	ARG	A	206	68.364	160.496	31.280	1.00	76.03	A	N
ATOM	1603	C	ARG	A	206	68.453	165.084	27.562	1.00	59.24	A	C
ATOM	1604	O	ARG	A	206	68.590	165.379	28.753	1.00	59.45	A	O
ATOM	1605	N	VAL	A	207	68.318	165.997	26.605	1.00	57.88	A	N
ATOM	1606	CA	VAL	A	207	68.304	167.427	26.900	1.00	55.96	A	C
ATOM	1607	CB	VAL	A	207	68.085	168.260	25.613	1.00	55.54	A	C
ATOM	1608	CG1	VAL	A	207	67.961	169.737	25.956	1.00	54.05	A	C
ATOM	1609	CG2	VAL	A	207	69.234	168.037	24.649	1.00	54.47	A	C
ATOM	1610	C	VAL	A	207	67.190	167.768	27.887	1.00	55.03	A	C
ATOM	1611	O	VAL	A	207	67.380	168.580	28.798	1.00	53.63	A	O
ATOM	1612	N	LEU	A	208	66.031	167.142	27.697	1.00	53.95	A	N
ATOM	1613	CA	LEU	A	208	64.865	167.378	28.546	1.00	53.14	A	C
ATOM	1614	CB	LEU	A	208	63.699	166.517	28.069	1.00	49.14	A	C
ATOM	1615	CG	LEU	A	208	63.286	166.583	26.596	1.00	48.06	A	C
ATOM	1616	CD1	LEU	A	208	62.131	165.616	26.366	1.00	44.36	A	C
ATOM	1617	CD2	LEU	A	208	62.880	168.004	26.217	1.00	43.79	A	C
ATOM	1618	C	LEU	A	208	65.145	167.062	30.016	1.00	56.19	A	C
ATOM	1619	O	LEU	A	208	64.456	167.547	30.918	1.00	55.47	A	O
ATOM	1620	N	ASP	A	209	66.162	166.244	30.248	1.00	58.60	A	N
ATOM	1621	CA	ASP	A	209	66.523	165.834	31.594	1.00	63.25	A	C
ATOM	1622	CB	ASP	A	209	67.227	164.475	31.537	1.00	65.73	A	C
ATOM	1623	CG	ASP	A	209	67.507	163.904	32.911	1.00	70.31	A	C
ATOM	1624	OD1	ASP	A	209	68.165	164.588	33.732	1.00	73.18	A	O
ATOM	1625	OD2	ASP	A	209	67.074	162.759	33.167	1.00	72.65	A	O
ATOM	1626	C	ASP	A	209	67.424	166.851	32.275	1.00	64.35	A	C
ATOM	1627	O	ASP	A	209	67.322	167.068	33.480	1.00	65.84	A	O
ATOM	1628	N	SER	A	210	68.303	167.469	31.493	1.00	66.00	A	N
ATOM	1629	CA	SER	A	210	69.251	168.453	31.997	1.00	66.92	A	C
ATOM	1630	CB	SER	A	210	69.735	169.350	30.855	1.00	66.58	A	C
ATOM	1631	OG	SER	A	210	70.668	170.310	31.324	1.00	67.27	A	O
ATOM	1632	C	SER	A	210	68.701	169.319	33.122	1.00	68.04	A	C
ATOM	1633	O	SER	A	210	67.615	169.890	33.018	1.00	68.19	A	O
ATOM	1634	N	LYS	A	211	69.466	169.412	34.202	1.00	69.67	A	N
ATOM	1635	CA	LYS	A	211	69.069	170.218	35.345	1.00	72.13	A	C
ATOM	1636	CB	LYS	A	211	69.533	169.554	36.652	1.00	73.31	A	C
ATOM	1637	CG	LYS	A	211	68.574	168.487	37.212	1.00	74.22	A	C
ATOM	1638	CD	LYS	A	211	68.397	167.293	36.271	1.00	75.60	A	C
ATOM	1639	CE	LYS	A	211	67.317	166.320	36.771	1.00	76.29	A	C
ATOM	1640	NZ	LYS	A	211	67.652	165.682	38.088	1.00	75.28	A	N
ATOM	1641	C	LYS	A	211	69.664	171.617	35.211	1.00	72.41	A	C
ATOM	1642	O	LYS	A	211	69.273	172.543	35.923	1.00	72.53	A	O
ATOM	1643	N	ASP	A	212	70.603	171.759	34.281	1.00	73.53	A	N
ATOM	1644	CA	ASP	A	212	71.267	173.032	34.023	1.00	73.50	A	C

FIGURE 11-37

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ATOM	1645	CB	ASP	A	212	72.236	172.872	32.852	1.00	75.61	A	C
ATOM	1646	CG	ASP	A	212	73.080	174.107	32.614	1.00	77.86	A	C
ATOM	1647	OD1	ASP	A	212	74.129	173.981	31.948	1.00	78.35	A	O
ATOM	1648	OD2	ASP	A	212	72.696	175.202	33.082	1.00	79.49	A	O
ATOM	1649	C	ASP	A	212	70.241	174.121	33.721	1.00	73.03	A	C
ATOM	1650	O	ASP	A	212	69.482	174.016	32.764	1.00	72.47	A	O
ATOM	1651	N	LYS	A	213	70.227	175.162	34.547	1.00	73.25	A	N
ATOM	1652	CA	LYS	A	213	69.289	176.275	34.403	1.00	73.82	A	C
ATOM	1653	CB	LYS	A	213	69.690	177.404	35.362	1.00	74.12	A	C
ATOM	1654	CG	LYS	A	213	68.720	178.575	35.420	1.00	77.03	A	C
ATOM	1655	CD	LYS	A	213	69.131	179.577	36.500	1.00	79.22	A	C
ATOM	1656	CE	LYS	A	213	68.140	180.739	36.613	1.00	80.57	A	C
ATOM	1657	NZ	LYS	A	213	68.546	181.734	37.654	1.00	79.97	A	N
ATOM	1658	C	LYS	A	213	69.197	176.810	32.971	1.00	73.46	A	C
ATOM	1659	O	LYS	A	213	68.137	177.252	32.523	1.00	73.54	A	O
ATOM	1660	N	LYS	A	214	70.313	176.756	32.256	1.00	72.89	A	N
ATOM	1661	CA	LYS	A	214	70.388	177.241	30.882	1.00	72.37	A	C
ATOM	1662	CB	LYS	A	214	71.838	177.119	30.394	1.00	74.84	A	C
ATOM	1663	CG	LYS	A	214	72.221	178.049	29.257	1.00	78.37	A	C
ATOM	1664	CD	LYS	A	214	73.734	178.026	29.019	1.00	80.61	A	C
ATOM	1665	CE	LYS	A	214	74.146	179.051	27.968	1.00	82.72	A	C
ATOM	1666	NZ	LYS	A	214	73.680	180.431	28.312	1.00	83.69	A	N
ATOM	1667	C	LYS	A	214	69.443	176.467	29.954	1.00	69.81	A	C
ATOM	1668	O	LYS	A	214	68.608	177.055	29.271	1.00	68.04	A	O
ATOM	1669	N	ASP	A	215	69.582	175.145	29.940	1.00	67.82	A	N
ATOM	1670	CA	ASP	A	215	68.756	174.281	29.105	1.00	65.51	A	C
ATOM	1671	CB	ASP	A	215	69.223	172.833	29.235	1.00	66.24	A	C
ATOM	1672	CG	ASP	A	215	70.688	172.659	28.882	1.00	68.51	A	C
ATOM	1673	OD1	ASP	A	215	71.079	173.033	27.755	1.00	70.20	A	O
ATOM	1674	OD2	ASP	A	215	71.451	172.143	29.728	1.00	68.27	A	O
ATOM	1675	C	ASP	A	215	67.276	174.360	29.469	1.00	64.23	A	C
ATOM	1676	O	ASP	A	215	66.412	174.503	28.595	1.00	63.25	A	O
ATOM	1677	N	LYS	A	216	67.001	174.268	30.767	1.00	61.74	A	N
ATOM	1678	CA	LYS	A	216	65.642	174.303	31.291	1.00	59.24	A	C
ATOM	1679	CB	LYS	A	216	65.671	174.415	32.818	1.00	60.21	A	C
ATOM	1680	CG	LYS	A	216	66.371	173.250	33.500	1.00	59.93	A	C
ATOM	1681	CD	LYS	A	216	66.053	173.196	34.985	1.00	61.36	A	C
ATOM	1682	CE	LYS	A	216	64.573	172.913	35.214	1.00	61.94	A	C
ATOM	1683	NZ	LYS	A	216	64.283	172.556	36.626	1.00	63.20	A	N
ATOM	1684	C	LYS	A	216	64.817	175.433	30.702	1.00	56.96	A	C
ATOM	1685	O	LYS	A	216	63.650	175.246	30.345	1.00	56.96	A	O
ATOM	1686	N	VAL	A	217	65.423	176.607	30.605	1.00	54.13	A	N
ATOM	1687	CA	VAL	A	217	64.736	177.753	30.037	1.00	51.74	A	C
ATOM	1688	CB	VAL	A	217	65.657	178.992	30.012	1.00	51.92	A	C
ATOM	1689	CG1	VAL	A	217	64.878	180.219	29.556	1.00	51.58	A	C
ATOM	1690	CG2	VAL	A	217	66.247	179.223	31.399	1.00	50.31	A	C
ATOM	1691	C	VAL	A	217	64.317	177.403	28.609	1.00	50.68	A	C
ATOM	1692	O	VAL	A	217	63.205	177.713	28.190	1.00	50.19	A	O
ATOM	1693	N	ILE	A	218	65.210	176.741	27.875	1.00	48.80	A	N
ATOM	1694	CA	ILE	A	218	64.936	176.357	26.495	1.00	47.34	A	C
ATOM	1695	CB	ILE	A	218	66.242	175.964	25.766	1.00	47.55	A	C
ATOM	1696	CG2	ILE	A	218	65.923	175.304	24.414	1.00	44.26	A	C
ATOM	1697	CG1	ILE	A	218	67.126	177.206	25.602	1.00	44.34	A	C
ATOM	1698	CD1	ILE	A	218	68.477	176.927	24.978	1.00	41.81	A	C
ATOM	1699	C	ILE	A	218	63.963	175.187	26.438	1.00	48.41	A	C
ATOM	1700	O	ILE	A	218	63.034	175.165	25.617	1.00	46.04	A	O
ATOM	1701	N	VAL	A	219	64.191	174.207	27.309	1.00	47.87	A	N
ATOM	1702	CA	VAL	A	219	63.338	173.031	27.381	1.00	45.39	A	C
ATOM	1703	CB	VAL	A	219	63.864	172.022	28.419	1.00	46.22	A	C
ATOM	1704	CG1	VAL	A	219	62.814	170.944	28.685	1.00	45.23	A	C
ATOM	1705	CG2	VAL	A	219	65.148	171.385	27.911	1.00	44.98	A	C

FIGURE 11-38

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ATOM	1706	C	VAL	A	219	61.924	173.434	27.763	1.00	45.43	A	C
ATOM	1707	O	VAL	A	219	60.962	172.772	27.380	1.00	46.50	A	O
ATOM	1708	N	ALA	A	220	61.795	174.525	28.509	1.00	43.99	A	N
ATOM	1709	CA	ALA	A	220	60.478	174.988	28.935	1.00	46.92	A	C
ATOM	1710	CB	ALA	A	220	60.607	176.292	29.734	1.00	44.24	A	C
ATOM	1711	C	ALA	A	220	59.487	175.177	27.780	1.00	49.68	A	C
ATOM	1712	O	ALA	A	220	58.280	175.025	27.970	1.00	50.02	A	O
ATOM	1713	N	GLU	A	221	59.983	175.518	26.591	1.00	51.83	A	N
ATOM	1714	CA	GLU	A	221	59.098	175.712	25.442	1.00	52.57	A	C
ATOM	1715	CB	GLU	A	221	59.303	177.106	24.830	1.00	56.57	A	C
ATOM	1716	CG	GLU	A	221	58.316	178.166	25.322	1.00	62.91	A	C
ATOM	1717	CD	GLU	A	221	58.573	178.614	26.754	1.00	68.08	A	C
ATOM	1718	OE1	GLU	A	221	59.629	179.237	27.005	1.00	70.51	A	O
ATOM	1719	OE2	GLU	A	221	57.720	178.347	27.633	1.00	70.30	A	O
ATOM	1720	C	GLU	A	221	59.279	174.639	24.367	1.00	50.42	A	C
ATOM	1721	O	GLU	A	221	58.750	174.756	23.261	1.00	49.92	A	O
ATOM	1722	N	ALA	A	222	60.027	173.594	24.696	1.00	48.12	A	N
ATOM	1723	CA	ALA	A	222	60.254	172.504	23.760	1.00	48.03	A	C
ATOM	1724	CB	ALA	A	222	61.295	171.556	24.319	1.00	45.35	A	C
ATOM	1725	C	ALA	A	222	58.951	171.744	23.473	1.00	48.10	A	C
ATOM	1726	O	ALA	A	222	57.967	171.861	24.210	1.00	48.50	A	O
ATOM	1727	N	PRO	A	223	58.920	170.962	22.384	1.00	47.02	A	N
ATOM	1728	CD	PRO	A	223	59.952	170.661	21.374	1.00	45.17	A	C
ATOM	1729	CA	PRO	A	223	57.686	170.229	22.102	1.00	45.77	A	C
ATOM	1730	CB	PRO	A	223	57.900	169.751	20.667	1.00	43.07	A	C
ATOM	1731	CG	PRO	A	223	59.363	169.458	20.653	1.00	42.95	A	C
ATOM	1732	C	PRO	A	223	57.560	169.074	23.098	1.00	45.16	A	C
ATOM	1733	O	PRO	A	223	58.575	168.543	23.568	1.00	43.52	A	O
ATOM	1734	N	SER	A	224	56.322	168.692	23.409	1.00	43.73	A	N
ATOM	1735	CA	SER	A	224	56.054	167.605	24.348	1.00	42.05	A	C
ATOM	1736	CB	SER	A	224	54.891	167.970	25.273	1.00	42.27	A	C
ATOM	1737	OG	SER	A	224	54.543	166.856	26.084	1.00	44.17	A	O
ATOM	1738	C	SER	A	224	55.737	166.277	23.676	1.00	41.10	A	C
ATOM	1739	O	SER	A	224	54.873	166.194	22.795	1.00	40.44	A	O
ATOM	1740	N	ILE	A	225	56.432	165.236	24.115	1.00	40.11	A	N
ATOM	1741	CA	ILE	A	225	56.229	163.902	23.582	1.00	40.52	A	C
ATOM	1742	CB	ILE	A	225	57.119	162.888	24.317	1.00	40.98	A	C
ATOM	1743	CG2	ILE	A	225	56.780	162.891	25.829	1.00	40.55	A	C
ATOM	1744	CG1	ILE	A	225	56.940	161.498	23.699	1.00	38.04	A	C
ATOM	1745	CD1	ILE	A	225	58.207	160.654	23.728	1.00	32.48	A	C
ATOM	1746	C	ILE	A	225	54.764	163.489	23.723	1.00	42.42	A	C
ATOM	1747	O	ILE	A	225	54.243	162.727	22.910	1.00	43.16	A	O
ATOM	1748	N	LEU	A	226	54.095	164.007	24.749	1.00	43.85	A	N
ATOM	1749	CA	LEU	A	226	52.687	163.681	24.976	1.00	45.32	A	C
ATOM	1750	CB	LEU	A	226	52.223	164.243	26.323	1.00	43.58	A	C
ATOM	1751	CG	LEU	A	226	53.011	163.691	27.511	1.00	43.44	A	C
ATOM	1752	CD1	LEU	A	226	52.546	164.365	28.788	1.00	42.05	A	C
ATOM	1753	CD2	LEU	A	226	52.834	162.180	27.587	1.00	44.45	A	C
ATOM	1754	C	LEU	A	226	51.783	164.195	23.859	1.00	46.11	A	C
ATOM	1755	O	LEU	A	226	50.691	163.672	23.645	1.00	45.53	A	O
ATOM	1756	N	ASP	A	227	52.234	165.225	23.151	1.00	49.08	A	N
ATOM	1757	CA	ASP	A	227	51.452	165.768	22.041	1.00	50.21	A	C
ATOM	1758	CB	ASP	A	227	51.689	167.271	21.888	1.00	49.47	A	C
ATOM	1759	CG	ASP	A	227	51.092	168.075	23.027	1.00	51.63	A	C
ATOM	1760	OD1	ASP	A	227	49.940	167.777	23.414	1.00	54.22	A	O
ATOM	1761	OD2	ASP	A	227	51.762	169.012	23.527	1.00	49.68	A	O
ATOM	1762	C	ASP	A	227	51.812	165.054	20.735	1.00	50.27	A	C
ATOM	1763	O	ASP	A	227	51.213	165.328	19.696	1.00	51.57	A	O
ATOM	1764	N	TYR	A	228	52.784	164.141	20.796	1.00	49.24	A	N
ATOM	1765	CA	TYR	A	228	53.219	163.387	19.623	1.00	48.49	A	C
ATOM	1766	CB	TYR	A	228	54.727	163.583	19.378	1.00	50.61	A	C

FIGURE 11-39

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ATOM	1767	CG	TYR	A	228	55.071	164.934	18.793	1.00	51.72	A	C
ATOM	1768	CD1	TYR	A	228	54.916	166.098	19.547	1.00	51.53	A	C
ATOM	1769	CE1	TYR	A	228	55.142	167.351	18.995	1.00	52.10	A	C
ATOM	1770	CD2	TYR	A	228	55.474	165.056	17.459	1.00	52.50	A	C
ATOM	1771	CE2	TYR	A	228	55.704	166.305	16.893	1.00	52.08	A	C
ATOM	1772	CZ	TYR	A	228	55.535	167.451	17.666	1.00	54.57	A	C
ATOM	1773	OH	TYR	A	228	55.762	168.698	17.122	1.00	53.05	A	O
ATOM	1774	C	TYR	A	228	52.918	161.899	19.724	1.00	49.61	A	C
ATOM	1775	O	TYR	A	228	53.315	161.121	18.859	1.00	50.68	A	O
ATOM	1776	N	LEU	A	229	52.225	161.495	20.784	1.00	50.89	A	N
ATOM	1777	CA	LEU	A	229	51.878	160.089	20.956	1.00	51.02	A	C
ATOM	1778	CB	LEU	A	229	51.078	159.880	22.248	1.00	48.82	A	C
ATOM	1779	CG	LEU	A	229	51.741	160.145	23.602	1.00	46.86	A	C
ATOM	1780	CD1	LEU	A	229	50.782	159.678	24.690	1.00	45.65	A	C
ATOM	1781	CD2	LEU	A	229	53.069	159.398	23.712	1.00	44.27	A	C
ATOM	1782	C	LEU	A	229	51.038	159.617	19.773	1.00	52.31	A	C
ATOM	1783	O	LEU	A	229	50.117	160.314	19.347	1.00	52.45	A	O
ATOM	1784	N	ASN	A	230	51.356	158.438	19.245	1.00	53.29	A	N
ATOM	1785	CA	ASN	A	230	50.603	157.889	18.127	1.00	54.75	A	C
ATOM	1786	CB	ASN	A	230	51.497	156.951	17.295	1.00	53.63	A	C
ATOM	1787	CG	ASN	A	230	51.674	155.584	17.923	1.00	53.58	A	C
ATOM	1788	OD1	ASN	A	230	51.850	155.452	19.129	1.00	53.82	A	O
ATOM	1789	ND2	ASN	A	230	51.645	154.553	17.093	1.00	56.08	A	N
ATOM	1790	C	ASN	A	230	49.373	157.158	18.685	1.00	56.37	A	C
ATOM	1791	O	ASN	A	230	49.239	157.006	19.895	1.00	56.21	A	O
ATOM	1792	N	GLU	A	231	48.484	156.718	17.801	1.00	57.69	A	N
ATOM	1793	CA	GLU	A	231	47.245	156.036	18.186	1.00	58.95	A	C
ATOM	1794	CB	GLU	A	231	46.665	155.290	16.977	1.00	64.39	A	C
ATOM	1795	CG	GLU	A	231	46.737	156.051	15.651	1.00	70.76	A	C
ATOM	1796	CD	GLU	A	231	47.374	155.219	14.539	1.00	73.99	A	C
ATOM	1797	OE1	GLU	A	231	48.619	155.054	14.555	1.00	75.29	A	O
ATOM	1798	OE2	GLU	A	231	46.628	154.724	13.658	1.00	74.41	A	O
ATOM	1799	C	GLU	A	231	47.332	155.063	19.373	1.00	56.03	A	C
ATOM	1800	O	GLU	A	231	46.727	155.291	20.420	1.00	55.11	A	O
ATOM	1801	N	PRO	A	232	48.075	153.959	19.223	1.00	53.05	A	N
ATOM	1802	CD	PRO	A	232	49.002	153.574	18.145	1.00	52.63	A	C
ATOM	1803	CA	PRO	A	232	48.161	153.020	20.343	1.00	52.18	A	C
ATOM	1804	CB	PRO	A	232	48.915	151.839	19.738	1.00	49.82	A	C
ATOM	1805	CG	PRO	A	232	49.870	152.517	18.819	1.00	52.34	A	C
ATOM	1806	C	PRO	A	232	48.851	153.608	21.581	1.00	50.81	A	C
ATOM	1807	O	PRO	A	232	48.452	153.321	22.705	1.00	50.39	A	O
ATOM	1808	N	SER	A	233	49.878	154.430	21.373	1.00	49.83	A	N
ATOM	1809	CA	SER	A	233	50.584	155.048	22.491	1.00	48.09	A	C
ATOM	1810	CB	SER	A	233	51.773	155.871	21.998	1.00	45.70	A	C
ATOM	1811	OG	SER	A	233	52.805	155.037	21.498	1.00	48.07	A	O
ATOM	1812	C	SER	A	233	49.632	155.961	23.252	1.00	49.22	A	C
ATOM	1813	O	SER	A	233	49.533	155.893	24.485	1.00	48.50	A	O
ATOM	1814	N	LYS	A	234	48.925	156.811	22.513	1.00	47.35	A	N
ATOM	1815	CA	LYS	A	234	47.999	157.733	23.135	1.00	47.85	A	C
ATOM	1816	CB	LYS	A	234	47.403	158.690	22.102	1.00	49.71	A	C
ATOM	1817	CG	LYS	A	234	46.468	159.717	22.718	1.00	52.04	A	C
ATOM	1818	CD	LYS	A	234	46.085	160.813	21.742	1.00	55.92	A	C
ATOM	1819	CE	LYS	A	234	45.235	161.873	22.444	1.00	59.68	A	C
ATOM	1820	NZ	LYS	A	234	44.854	163.024	21.560	1.00	62.15	A	N
ATOM	1821	C	LYS	A	234	46.886	156.990	23.848	1.00	48.30	A	C
ATOM	1822	O	LYS	A	234	46.452	157.398	24.921	1.00	49.33	A	O
ATOM	1823	N	ALA	A	235	46.426	155.895	23.260	1.00	47.24	A	N
ATOM	1824	CA	ALA	A	235	45.354	155.124	23.863	1.00	47.65	A	C
ATOM	1825	CB	ALA	A	235	44.861	154.074	22.875	1.00	47.76	A	C
ATOM	1826	C	ALA	A	235	45.805	154.456	25.170	1.00	47.64	A	C
ATOM	1827	O	ALA	A	235	45.038	154.371	26.134	1.00	47.13	A	O

FIGURE 11-40

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ATOM	1828	N	HIS	A	236	47.051	153.992	25.198	1.00	45.43	A	N
ATOM	1829	CA	HIS	A	236	47.600	153.325	26.374	1.00	44.75	A	C
ATOM	1830	CB	HIS	A	236	48.935	152.672	26.024	1.00	44.69	A	C
ATOM	1831	CG	HIS	A	236	49.522	151.854	27.132	1.00	47.07	A	C
ATOM	1832	CD2	HIS	A	236	50.354	152.192	28.145	1.00	47.20	A	C
ATOM	1833	ND1	HIS	A	236	49.279	150.504	27.270	1.00	48.97	A	N
ATOM	1834	CE1	HIS	A	236	49.940	150.043	28.317	1.00	47.58	A	C
ATOM	1835	NE2	HIS	A	236	50.600	151.047	28.866	1.00	49.26	A	N
ATOM	1836	C	HIS	A	236	47.801	154.315	27.521	1.00	44.38	A	C
ATOM	1837	O	HIS	A	236	47.416	154.047	28.657	1.00	43.16	A	O
ATOM	1838	N	PHE	A	237	48.403	155.458	27.211	1.00	44.01	A	N
ATOM	1839	CA	PHE	A	237	48.665	156.491	28.201	1.00	44.22	A	C
ATOM	1840	CB	PHE	A	237	49.430	157.644	27.561	1.00	44.29	A	C
ATOM	1841	CG	PHE	A	237	49.853	158.696	28.536	1.00	45.02	A	C
ATOM	1842	CD1	PHE	A	237	50.747	158.387	29.567	1.00	47.16	A	C
ATOM	1843	CD2	PHE	A	237	49.320	159.978	28.466	1.00	43.93	A	C
ATOM	1844	CE1	PHE	A	237	51.100	159.340	30.522	1.00	47.59	A	C
ATOM	1845	CE2	PHE	A	237	49.662	160.942	29.412	1.00	48.16	A	C
ATOM	1846	CZ	PHE	A	237	50.556	160.624	30.447	1.00	47.82	A	C
ATOM	1847	C	PHE	A	237	47.363	157.008	28.792	1.00	46.46	A	C
ATOM	1848	O	PHE	A	237	47.239	157.193	30.009	1.00	48.01	A	O
ATOM	1849	N	GLU	A	238	46.387	157.244	27.924	1.00	45.83	A	N
ATOM	1850	CA	GLU	A	238	45.090	157.736	28.363	1.00	44.55	A	C
ATOM	1851	CB	GLU	A	238	44.223	158.049	27.143	1.00	44.71	A	C
ATOM	1852	CG	GLU	A	238	43.804	159.500	27.007	1.00	49.12	A	C
ATOM	1853	CD	GLU	A	238	43.485	159.874	25.565	1.00	52.99	A	C
ATOM	1854	OE1	GLU	A	238	42.773	159.097	24.882	1.00	55.28	A	O
ATOM	1855	OE2	GLU	A	238	43.949	160.944	25.114	1.00	54.08	A	O
ATOM	1856	C	GLU	A	238	44.399	156.706	29.270	1.00	43.21	A	C
ATOM	1857	O	GLU	A	238	43.670	157.072	30.199	1.00	39.96	A	O
ATOM	1858	N	ALA	A	239	44.614	155.421	28.993	1.00	41.20	A	N
ATOM	1859	CA	ALA	A	239	44.014	154.374	29.822	1.00	41.28	A	C
ATOM	1860	CB	ALA	A	239	44.275	152.995	29.223	1.00	38.95	A	C
ATOM	1861	C	ALA	A	239	44.664	154.480	31.198	1.00	40.30	A	C
ATOM	1862	O	ALA	A	239	43.987	154.502	32.217	1.00	39.34	A	O
ATOM	1863	N	VAL	A	240	45.990	154.558	31.206	1.00	39.96	A	N
ATOM	1864	CA	VAL	A	240	46.742	154.689	32.443	1.00	38.87	A	C
ATOM	1865	CB	VAL	A	240	48.232	154.976	32.149	1.00	37.72	A	C
ATOM	1866	CG1	VAL	A	240	48.937	155.529	33.409	1.00	37.23	A	C
ATOM	1867	CG2	VAL	A	240	48.910	153.696	31.685	1.00	32.72	A	C
ATOM	1868	C	VAL	A	240	46.177	155.813	33.310	1.00	39.91	A	C
ATOM	1869	O	VAL	A	240	45.730	155.571	34.428	1.00	39.74	A	O
ATOM	1870	N	THR	A	241	46.185	157.034	32.779	1.00	40.88	A	N
ATOM	1871	CA	THR	A	241	45.704	158.199	33.509	1.00	42.70	A	C
ATOM	1872	CB	THR	A	241	45.959	159.496	32.721	1.00	44.24	A	C
ATOM	1873	OG1	THR	A	241	45.151	159.511	31.536	1.00	47.49	A	O
ATOM	1874	CG2	THR	A	241	47.425	159.590	32.334	1.00	44.56	A	C
ATOM	1875	C	THR	A	241	44.227	158.141	33.869	1.00	42.98	A	C
ATOM	1876	O	THR	A	241	43.806	158.703	34.884	1.00	43.26	A	O
ATOM	1877	N	ASP	A	242	43.436	157.472	33.040	1.00	42.52	A	N
ATOM	1878	CA	ASP	A	242	42.023	157.357	33.327	1.00	43.18	A	C
ATOM	1879	CB	ASP	A	242	41.283	156.755	32.138	1.00	48.65	A	C
ATOM	1880	CG	ASP	A	242	39.851	156.377	32.471	1.00	56.92	A	C
ATOM	1881	OD1	ASP	A	242	39.088	157.263	32.936	1.00	61.27	A	O
ATOM	1882	OD2	ASP	A	242	39.485	155.192	32.270	1.00	58.83	A	O
ATOM	1883	C	ASP	A	242	41.881	156.465	34.549	1.00	43.08	A	C
ATOM	1884	O	ASP	A	242	41.087	156.742	35.446	1.00	42.30	A	O
ATOM	1885	N	MET	A	243	42.675	155.402	34.594	1.00	42.32	A	N
ATOM	1886	CA	MET	A	243	42.611	154.489	35.715	1.00	43.01	A	C
ATOM	1887	CB	MET	A	243	43.300	153.176	35.373	1.00	43.71	A	C
ATOM	1888	CG	MET	A	243	42.382	152.212	34.644	1.00	44.82	A	C

FIGURE 11-41

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ATOM	1889	SD	MET	A	243	43.259	150.777	34.012	1.00	53.14	A	S
ATOM	1890	CE	MET	A	243	44.131	151.513	32.686	1.00	45.31	A	C
ATOM	1891	C	MET	A	243	43.163	155.065	37.007	1.00	41.91	A	C
ATOM	1892	O	MET	A	243	42.620	154.786	38.078	1.00	41.64	A	O
ATOM	1893	N	LEU	A	244	44.232	155.854	36.917	1.00	38.70	A	N
ATOM	1894	CA	LEU	A	244	44.798	156.476	38.109	1.00	38.01	A	C
ATOM	1895	CB	LEU	A	244	46.086	157.231	37.765	1.00	35.33	A	C
ATOM	1896	CG	LEU	A	244	47.306	156.382	37.399	1.00	31.45	A	C
ATOM	1897	CD1	LEU	A	244	48.302	157.227	36.642	1.00	27.54	A	C
ATOM	1898	CD2	LEU	A	244	47.927	155.795	38.656	1.00	27.25	A	C
ATOM	1899	C	LEU	A	244	43.747	157.449	38.658	1.00	39.12	A	C
ATOM	1900	O	LEU	A	244	43.585	157.592	39.873	1.00	39.25	A	O
ATOM	1901	N	ASP	A	245	43.030	158.106	37.748	1.00	39.96	A	N
ATOM	1902	CA	ASP	A	245	41.983	159.048	38.127	1.00	41.10	A	C
ATOM	1903	CB	ASP	A	245	41.346	159.676	36.881	1.00	39.87	A	C
ATOM	1904	CG	ASP	A	245	42.235	160.732	36.206	1.00	41.11	A	C
ATOM	1905	OD1	ASP	A	245	41.785	161.291	35.183	1.00	38.29	A	O
ATOM	1906	OD2	ASP	A	245	43.361	161.016	36.681	1.00	38.84	A	O
ATOM	1907	C	ASP	A	245	40.895	158.309	38.914	1.00	44.05	A	C
ATOM	1908	O	ASP	A	245	40.509	158.720	40.021	1.00	45.99	A	O
ATOM	1909	N	LEU	A	246	40.414	157.212	38.334	1.00	43.44	A	N
ATOM	1910	CA	LEU	A	246	39.356	156.406	38.927	1.00	44.76	A	C
ATOM	1911	CB	LEU	A	246	38.934	155.311	37.942	1.00	46.02	A	C
ATOM	1912	CG	LEU	A	246	38.136	155.895	36.760	1.00	48.83	A	C
ATOM	1913	CD1	LEU	A	246	37.873	154.845	35.688	1.00	47.78	A	C
ATOM	1914	CD2	LEU	A	246	36.822	156.452	37.290	1.00	48.55	A	C
ATOM	1915	C	LEU	A	246	39.702	155.810	40.288	1.00	45.26	A	C
ATOM	1916	O	LEU	A	246	38.834	155.668	41.151	1.00	45.88	A	O
ATOM	1917	N	LEU	A	247	40.967	155.461	40.484	1.00	44.51	A	N
ATOM	1918	CA	LEU	A	247	41.397	154.920	41.761	1.00	42.37	A	C
ATOM	1919	CB	LEU	A	247	42.648	154.057	41.595	1.00	40.94	A	C
ATOM	1920	CG	LEU	A	247	42.508	152.725	40.863	1.00	40.20	A	C
ATOM	1921	CD1	LEU	A	247	43.889	152.057	40.791	1.00	40.80	A	C
ATOM	1922	CD2	LEU	A	247	41.509	151.825	41.588	1.00	35.95	A	C
ATOM	1923	C	LEU	A	247	41.706	156.101	42.679	1.00	41.79	A	C
ATOM	1924	O	LEU	A	247	42.085	155.919	43.833	1.00	37.44	A	O
ATOM	1925	N	GLU	A	248	41.542	157.312	42.147	1.00	42.22	A	N
ATOM	1926	CA	GLU	A	248	41.796	158.536	42.904	1.00	43.78	A	C
ATOM	1927	CB	GLU	A	248	40.787	158.648	44.055	1.00	44.84	A	C
ATOM	1928	CG	GLU	A	248	39.400	159.016	43.540	1.00	51.18	A	C
ATOM	1929	CD	GLU	A	248	38.302	158.922	44.582	1.00	53.48	A	C
ATOM	1930	OE1	GLU	A	248	37.123	159.109	44.205	1.00	56.91	A	O
ATOM	1931	OE2	GLU	A	248	38.605	158.666	45.767	1.00	56.74	A	O
ATOM	1932	C	GLU	A	248	43.233	158.662	43.412	1.00	42.78	A	C
ATOM	1933	O	GLU	A	248	43.497	159.284	44.443	1.00	43.34	A	O
ATOM	1934	N	ILE	A	249	44.163	158.065	42.672	1.00	40.91	A	N
ATOM	1935	CA	ILE	A	249	45.571	158.141	43.014	1.00	39.47	A	C
ATOM	1936	CB	ILE	A	249	46.337	156.946	42.424	1.00	40.06	A	C
ATOM	1937	CG2	ILE	A	249	47.844	157.194	42.475	1.00	37.52	A	C
ATOM	1938	CG1	ILE	A	249	45.939	155.676	43.172	1.00	37.43	A	C
ATOM	1939	CD1	ILE	A	249	46.515	154.412	42.562	1.00	39.78	A	C
ATOM	1940	C	ILE	A	249	46.127	159.449	42.436	1.00	38.74	A	C
ATOM	1941	O	ILE	A	249	46.105	159.663	41.233	1.00	38.43	A	O
ATOM	1942	N	PRO	A	250	46.618	160.349	43.295	1.00	38.60	A	N
ATOM	1943	CD	PRO	A	250	46.810	160.262	44.757	1.00	40.25	A	C
ATOM	1944	CA	PRO	A	250	47.152	161.602	42.756	1.00	38.89	A	C
ATOM	1945	CB	PRO	A	250	47.345	162.459	44.005	1.00	39.14	A	C
ATOM	1946	CG	PRO	A	250	47.748	161.431	45.053	1.00	38.07	A	C
ATOM	1947	C	PRO	A	250	48.462	161.347	42.019	1.00	38.43	A	C
ATOM	1948	O	PRO	A	250	49.233	160.469	42.395	1.00	39.64	A	O
ATOM	1949	N	TYR	A	251	48.715	162.105	40.966	1.00	36.82	A	N

FIGURE 11-42

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ATOM	1950	CA	TYR	A	251	49.950	161.932	40.231	1.00	38.11	A	C
ATOM	1951	CB	TYR	A	251	49.860	160.716	39.306	1.00	36.94	A	C
ATOM	1952	CG	TYR	A	251	48.793	160.880	38.270	1.00	35.42	A	C
ATOM	1953	CD1	TYR	A	251	49.080	161.456	37.032	1.00	33.28	A	C
ATOM	1954	CE1	TYR	A	251	48.075	161.703	36.113	1.00	35.50	A	C
ATOM	1955	CD2	TYR	A	251	47.474	160.549	38.561	1.00	33.83	A	C
ATOM	1956	CE2	TYR	A	251	46.463	160.795	37.654	1.00	34.87	A	C
ATOM	1957	CZ	TYR	A	251	46.767	161.373	36.435	1.00	34.84	A	C
ATOM	1958	OH	TYR	A	251	45.753	161.646	35.561	1.00	36.98	A	O
ATOM	1959	C	TYR	A	251	50.253	163.182	39.429	1.00	39.72	A	C
ATOM	1960	O	TYR	A	251	49.414	164.066	39.274	1.00	39.06	A	O
ATOM	1961	N	GLU	A	252	51.467	163.232	38.907	1.00	42.19	A	N
ATOM	1962	CA	GLU	A	252	51.930	164.371	38.154	1.00	42.60	A	C
ATOM	1963	CB	GLU	A	252	53.036	165.042	38.955	1.00	46.13	A	C
ATOM	1964	CG	GLU	A	252	53.154	166.528	38.812	1.00	49.71	A	C
ATOM	1965	CD	GLU	A	252	54.232	167.080	39.726	1.00	53.23	A	C
ATOM	1966	OE1	GLU	A	252	55.433	166.938	39.394	1.00	52.30	A	O
ATOM	1967	OE2	GLU	A	252	53.872	167.638	40.785	1.00	53.17	A	O
ATOM	1968	C	GLU	A	252	52.473	163.876	36.823	1.00	43.46	A	C
ATOM	1969	O	GLU	A	252	53.171	162.856	36.757	1.00	42.51	A	O
ATOM	1970	N	ILE	A	253	52.141	164.598	35.762	1.00	44.24	A	N
ATOM	1971	CA	ILE	A	253	52.607	164.252	34.432	1.00	43.04	A	C
ATOM	1972	CB	ILE	A	253	51.509	164.483	33.393	1.00	43.50	A	C
ATOM	1973	CG2	ILE	A	253	52.040	164.148	32.007	1.00	43.95	A	C
ATOM	1974	CG1	ILE	A	253	50.285	163.631	33.739	1.00	42.76	A	C
ATOM	1975	CD1	ILE	A	253	49.077	163.868	32.837	1.00	42.19	A	C
ATOM	1976	C	ILE	A	253	53.778	165.169	34.120	1.00	42.76	A	C
ATOM	1977	O	ILE	A	253	53.630	166.386	34.138	1.00	43.10	A	O
ATOM	1978	N	ASP	A	254	54.942	164.587	33.856	1.00	41.99	A	N
ATOM	1979	CA	ASP	A	254	56.142	165.364	33.540	1.00	41.02	A	C
ATOM	1980	CB	ASP	A	254	57.229	165.105	34.589	1.00	41.35	A	C
ATOM	1981	CG	ASP	A	254	58.457	165.988	34.409	1.00	43.76	A	C
ATOM	1982	OD1	ASP	A	254	59.450	165.801	35.159	1.00	45.98	A	O
ATOM	1983	OD2	ASP	A	254	58.438	166.872	33.523	1.00	47.92	A	O
ATOM	1984	C	ASP	A	254	56.628	164.920	32.159	1.00	38.73	A	C
ATOM	1985	O	ASP	A	254	57.327	163.918	32.036	1.00	37.12	A	O
ATOM	1986	N	SER	A	255	56.245	165.669	31.131	1.00	38.14	A	N
ATOM	1987	CA	SER	A	255	56.616	165.339	29.761	1.00	40.64	A	C
ATOM	1988	CB	SER	A	255	55.960	166.307	28.779	1.00	41.15	A	C
ATOM	1989	OG	SER	A	255	56.476	167.618	28.925	1.00	45.62	A	O
ATOM	1990	C	SER	A	255	58.117	165.352	29.548	1.00	41.47	A	C
ATOM	1991	O	SER	A	255	58.613	164.762	28.599	1.00	40.76	A	O
ATOM	1992	N	ASN	A	256	58.844	166.012	30.437	1.00	43.91	A	N
ATOM	1993	CA	ASN	A	256	60.285	166.066	30.299	1.00	47.74	A	C
ATOM	1994	CB	ASN	A	256	60.792	167.448	30.697	1.00	50.34	A	C
ATOM	1995	CG	ASN	A	256	60.225	168.533	29.804	1.00	52.44	A	C
ATOM	1996	OD1	ASN	A	256	59.976	169.658	30.246	1.00	54.28	A	O
ATOM	1997	ND2	ASN	A	256	60.012	168.196	28.531	1.00	50.64	A	N
ATOM	1998	C	ASN	A	256	60.976	164.977	31.096	1.00	49.10	A	C
ATOM	1999	O	ASN	A	256	62.198	164.815	31.011	1.00	49.33	A	O
ATOM	2000	N	MET	A	257	60.203	164.217	31.864	1.00	49.50	A	N
ATOM	2001	CA	MET	A	257	60.800	163.129	32.611	1.00	50.36	A	C
ATOM	2002	CB	MET	A	257	59.841	162.588	33.666	1.00	52.44	A	C
ATOM	2003	CG	MET	A	257	60.524	161.701	34.695	1.00	52.97	A	C
ATOM	2004	SD	MET	A	257	59.790	160.076	34.770	1.00	54.19	A	S
ATOM	2005	CE	MET	A	257	58.412	160.445	35.825	1.00	55.24	A	C
ATOM	2006	C	MET	A	257	61.118	162.050	31.582	1.00	51.20	A	C
ATOM	2007	O	MET	A	257	60.227	161.439	30.998	1.00	49.87	A	O
ATOM	2008	N	VAL	A	258	62.407	161.870	31.334	1.00	52.96	A	N
ATOM	2009	CA	VAL	A	258	62.897	160.884	30.385	1.00	53.44	A	C
ATOM	2010	CB	VAL	A	258	63.615	161.565	29.175	1.00	52.19	A	C

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ATOM	2011	CG1	VAL	A	258	62.677	162.561	28.517	1.00	52.25	A	C
ATOM	2012	CG2	VAL	A	258	64.879	162.275	29.627	1.00	51.20	A	C
ATOM	2013	C	VAL	A	258	63.883	160.047	31.190	1.00	55.12	A	C
ATOM	2014	O	VAL	A	258	64.479	160.537	32.154	1.00	57.11	A	O
ATOM	2015	N	ARG	A	259	64.056	158.793	30.806	1.00	54.41	A	N
ATOM	2016	CA	ARG	A	259	64.942	157.906	31.537	1.00	55.13	A	C
ATOM	2017	CB	ARG	A	259	64.521	157.866	33.018	1.00	55.11	A	C
ATOM	2018	CG	ARG	A	259	65.355	156.958	33.929	1.00	56.72	A	C
ATOM	2019	CD	ARG	A	259	64.884	157.084	35.389	1.00	55.07	A	C
ATOM	2020	NE	ARG	A	259	63.435	156.947	35.458	1.00	53.64	A	N
ATOM	2021	CZ	ARG	A	259	62.791	155.788	35.473	1.00	48.85	A	C
ATOM	2022	NH1	ARG	A	259	63.469	154.650	35.450	1.00	47.38	A	N
ATOM	2023	NH2	ARG	A	259	61.467	155.774	35.450	1.00	47.50	A	N
ATOM	2024	C	ARG	A	259	64.731	156.555	30.891	1.00	54.37	A	C
ATOM	2025	O	ARG	A	259	63.616	156.249	30.471	1.00	55.90	A	O
ATOM	2026	N	GLY	A	260	65.784	155.751	30.803	1.00	52.29	A	N
ATOM	2027	CA	GLY	A	260	65.640	154.446	30.184	1.00	51.00	A	C
ATOM	2028	C	GLY	A	260	65.207	154.585	28.735	1.00	51.11	A	C
ATOM	2029	O	GLY	A	260	64.488	153.737	28.200	1.00	49.52	A	O
ATOM	2030	N	LEU	A	261	65.656	155.663	28.099	1.00	51.53	A	N
ATOM	2031	CA	LEU	A	261	65.322	155.950	26.705	1.00	53.71	A	C
ATOM	2032	CB	LEU	A	261	66.153	157.137	26.209	1.00	52.31	A	C
ATOM	2033	CG	LEU	A	261	65.914	158.403	27.025	1.00	51.10	A	C
ATOM	2034	CD1	LEU	A	261	66.781	159.520	26.506	1.00	51.73	A	C
ATOM	2035	CD2	LEU	A	261	64.436	158.777	26.958	1.00	51.00	A	C
ATOM	2036	C	LEU	A	261	65.548	154.756	25.792	1.00	52.51	A	C
ATOM	2037	O	LEU	A	261	64.756	154.483	24.898	1.00	52.23	A	O
ATOM	2038	N	ASP	A	262	66.633	154.043	26.044	1.00	53.17	A	N
ATOM	2039	CA	ASP	A	262	67.000	152.877	25.258	1.00	53.62	A	C
ATOM	2040	CB	ASP	A	262	68.408	152.437	25.653	1.00	56.86	A	C
ATOM	2041	CG	ASP	A	262	69.472	153.440	25.236	1.00	60.18	A	C
ATOM	2042	OD1	ASP	A	262	69.245	154.664	25.381	1.00	62.36	A	O
ATOM	2043	OD2	ASP	A	262	70.545	152.998	24.771	1.00	62.14	A	O
ATOM	2044	C	ASP	A	262	66.061	151.669	25.337	1.00	52.22	A	C
ATOM	2045	O	ASP	A	262	65.932	150.934	24.360	1.00	53.21	A	O
ATOM	2046	N	TYR	A	263	65.394	151.464	26.472	1.00	49.69	A	N
ATOM	2047	CA	TYR	A	263	64.531	150.289	26.623	1.00	45.91	A	C
ATOM	2048	CB	TYR	A	263	65.166	149.335	27.632	1.00	45.72	A	C
ATOM	2049	CG	TYR	A	263	65.426	149.975	28.976	1.00	46.21	A	C
ATOM	2050	CD1	TYR	A	263	64.437	150.022	29.956	1.00	44.81	A	C
ATOM	2051	CE1	TYR	A	263	64.674	150.624	31.182	1.00	46.17	A	C
ATOM	2052	CD2	TYR	A	263	66.662	150.549	29.261	1.00	46.02	A	C
ATOM	2053	CE2	TYR	A	263	66.909	151.152	30.483	1.00	47.09	A	C
ATOM	2054	CZ	TYR	A	263	65.911	151.186	31.440	1.00	46.59	A	C
ATOM	2055	OH	TYR	A	263	66.160	151.778	32.650	1.00	45.79	A	O
ATOM	2056	C	TYR	A	263	63.065	150.479	26.994	1.00	43.85	A	C
ATOM	2057	O	TYR	A	263	62.230	149.646	26.653	1.00	41.94	A	O
ATOM	2058	N	TYR	A	264	62.749	151.553	27.702	1.00	42.56	A	N
ATOM	2059	CA	TYR	A	264	61.374	151.799	28.111	1.00	43.02	A	C
ATOM	2060	CB	TYR	A	264	61.309	152.978	29.079	1.00	41.79	A	C
ATOM	2061	CG	TYR	A	264	61.610	152.653	30.519	1.00	44.61	A	C
ATOM	2062	CD1	TYR	A	264	62.414	153.508	31.285	1.00	44.29	A	C
ATOM	2063	CE1	TYR	A	264	62.652	153.258	32.633	1.00	44.67	A	C
ATOM	2064	CD2	TYR	A	264	61.050	151.530	31.141	1.00	43.73	A	C
ATOM	2065	CE2	TYR	A	264	61.278	151.270	32.499	1.00	44.64	A	C
ATOM	2066	CZ	TYR	A	264	62.079	152.142	33.235	1.00	45.64	A	C
ATOM	2067	OH	TYR	A	264	62.284	151.935	34.575	1.00	47.85	A	O
ATOM	2068	C	TYR	A	264	60.431	152.097	26.953	1.00	43.01	A	C
ATOM	2069	O	TYR	A	264	60.800	152.724	25.960	1.00	45.02	A	O
ATOM	2070	N	THR	A	265	59.195	151.662	27.106	1.00	42.16	A	N
ATOM	2071	CA	THR	A	265	58.175	151.922	26.115	1.00	43.62	A	C

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ATOM	2072	CB	THR	A	265	57.824	150.662	25.309	1.00	44.70	A	C
ATOM	2073	OG1	THR	A	265	58.941	150.303	24.485	1.00	46.57	A	O
ATOM	2074	CG2	THR	A	265	56.639	150.931	24.409	1.00	46.29	A	C
ATOM	2075	C	THR	A	265	56.940	152.398	26.851	1.00	43.12	A	C
ATOM	2076	O	THR	A	265	56.632	151.924	27.948	1.00	46.64	A	O
ATOM	2077	N	HIS	A	266	56.242	153.353	26.259	1.00	41.33	A	N
ATOM	2078	CA	HIS	A	266	55.035	153.877	26.862	1.00	41.26	A	C
ATOM	2079	CB	HIS	A	266	53.952	152.802	26.834	1.00	39.01	A	C
ATOM	2080	CG	HIS	A	266	53.574	152.395	25.447	1.00	43.06	A	C
ATOM	2081	CD2	HIS	A	266	52.982	153.093	24.448	1.00	40.31	A	C
ATOM	2082	ND1	HIS	A	266	53.904	151.168	24.913	1.00	42.58	A	N
ATOM	2083	CE1	HIS	A	266	53.534	151.129	23.645	1.00	42.69	A	C
ATOM	2084	NE2	HIS	A	266	52.974	152.286	23.337	1.00	41.05	A	N
ATOM	2085	C	HIS	A	266	55.217	154.436	28.277	1.00	40.48	A	C
ATOM	2086	O	HIS	A	266	56.007	155.355	28.492	1.00	41.50	A	O
ATOM	2087	N	THR	A	267	54.497	153.872	29.234	1.00	38.19	A	N
ATOM	2088	CA	THR	A	267	54.534	154.359	30.602	1.00	36.18	A	C
ATOM	2089	CB	THR	A	267	53.478	153.645	31.483	1.00	37.66	A	C
ATOM	2090	OG1	THR	A	267	52.228	153.578	30.790	1.00	35.85	A	O
ATOM	2091	CG2	THR	A	267	53.277	154.414	32.798	1.00	36.57	A	C
ATOM	2092	C	THR	A	267	55.838	154.260	31.362	1.00	33.88	A	C
ATOM	2093	O	THR	A	267	56.445	153.200	31.437	1.00	35.74	A	O
ATOM	2094	N	ILE	A	268	56.275	155.381	31.918	1.00	33.59	A	N
ATOM	2095	CA	ILE	A	268	57.448	155.373	32.784	1.00	34.14	A	C
ATOM	2096	CB	ILE	A	268	58.704	155.959	32.150	1.00	34.70	A	C
ATOM	2097	CG2	ILE	A	268	59.302	154.948	31.189	1.00	35.82	A	C
ATOM	2098	CG1	ILE	A	268	58.383	157.305	31.530	1.00	35.73	A	C
ATOM	2099	CD1	ILE	A	268	59.630	158.111	31.244	1.00	38.98	A	C
ATOM	2100	C	ILE	A	268	57.046	156.230	33.963	1.00	31.03	A	C
ATOM	2101	O	ILE	A	268	56.192	157.123	33.830	1.00	27.65	A	O
ATOM	2102	N	PHE	A	269	57.661	155.983	35.110	1.00	27.88	A	N
ATOM	2103	CA	PHE	A	269	57.272	156.728	36.288	1.00	30.96	A	C
ATOM	2104	CB	PHE	A	269	56.018	156.087	36.916	1.00	29.17	A	C
ATOM	2105	CG	PHE	A	269	56.334	154.849	37.734	1.00	29.97	A	C
ATOM	2106	CD1	PHE	A	269	56.561	153.625	37.111	1.00	27.40	A	C
ATOM	2107	CD2	PHE	A	269	56.509	154.941	39.117	1.00	27.48	A	C
ATOM	2108	CE1	PHE	A	269	56.960	152.518	37.844	1.00	28.40	A	C
ATOM	2109	CE2	PHE	A	269	56.908	153.844	39.862	1.00	28.18	A	C
ATOM	2110	CZ	PHE	A	269	57.136	152.630	39.228	1.00	32.39	A	C
ATOM	2111	C	PHE	A	269	58.340	156.746	37.361	1.00	31.68	A	C
ATOM	2112	O	PHE	A	269	59.272	155.939	37.367	1.00	29.84	A	O
ATOM	2113	N	GLU	A	270	58.157	157.667	38.294	1.00	32.65	A	N
ATOM	2114	CA	GLU	A	270	59.041	157.773	39.442	1.00	34.38	A	C
ATOM	2115	CB	GLU	A	270	60.150	158.800	39.201	1.00	33.58	A	C
ATOM	2116	CG	GLU	A	270	61.092	158.431	38.083	1.00	39.77	A	C
ATOM	2117	CD	GLU	A	270	62.214	159.440	37.888	1.00	42.12	A	C
ATOM	2118	OE1	GLU	A	270	62.862	159.379	36.821	1.00	42.35	A	O
ATOM	2119	OE2	GLU	A	270	62.453	160.280	38.791	1.00	40.63	A	O
ATOM	2120	C	GLU	A	270	58.182	158.225	40.607	1.00	31.87	A	C
ATOM	2121	O	GLU	A	270	57.204	158.939	40.422	1.00	29.87	A	O
ATOM	2122	N	ILE	A	271	58.504	157.748	41.796	1.00	31.42	A	N
ATOM	2123	CA	ILE	A	271	57.800	158.199	42.978	1.00	32.23	A	C
ATOM	2124	CB	ILE	A	271	57.453	157.044	43.923	1.00	32.49	A	C
ATOM	2125	CG2	ILE	A	271	57.019	157.605	45.286	1.00	31.85	A	C
ATOM	2126	CG1	ILE	A	271	56.319	156.207	43.312	1.00	32.84	A	C
ATOM	2127	CD1	ILE	A	271	56.120	154.854	43.974	1.00	29.35	A	C
ATOM	2128	C	ILE	A	271	58.855	159.092	43.606	1.00	33.01	A	C
ATOM	2129	O	ILE	A	271	59.993	158.672	43.802	1.00	34.41	A	O
ATOM	2130	N	MET	A	272	58.514	160.331	43.904	1.00	33.73	A	N
ATOM	2131	CA	MET	A	272	59.531	161.194	44.469	1.00	36.83	A	C
ATOM	2132	CB	MET	A	272	59.761	162.382	43.541	1.00	40.75	A	C

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ATOM	2133	CG	MET	A	272	59.942	161.942	42.097	1.00	45.07	A	C
ATOM	2134	SD	MET	A	272	60.718	163.201	41.135	1.00	56.85	A	S
ATOM	2135	CE	MET	A	272	59.358	164.191	40.631	1.00	51.79	A	C
ATOM	2136	C	MET	A	272	59.231	161.680	45.863	1.00	37.48	A	C
ATOM	2137	O	MET	A	272	58.084	161.977	46.205	1.00	37.42	A	O
ATOM	2138	N	SER	A	273	60.272	161.745	46.678	1.00	36.44	A	N
ATOM	2139	CA	SER	A	273	60.102	162.231	48.023	1.00	37.02	A	C
ATOM	2140	CB	SER	A	273	61.230	161.756	48.924	1.00	35.76	A	C
ATOM	2141	OG	SER	A	273	61.299	162.589	50.073	1.00	37.80	A	O
ATOM	2142	C	SER	A	273	60.107	163.742	47.966	1.00	38.67	A	C
ATOM	2143	O	SER	A	273	60.936	164.348	47.274	1.00	37.68	A	O
ATOM	2144	N	GLU	A	274	59.165	164.347	48.679	1.00	39.90	A	N
ATOM	2145	CA	GLU	A	274	59.070	165.795	48.735	1.00	42.93	A	C
ATOM	2146	CB	GLU	A	274	57.631	166.247	48.496	1.00	45.93	A	C
ATOM	2147	CG	GLU	A	274	57.109	165.912	47.111	1.00	51.75	A	C
ATOM	2148	CD	GLU	A	274	55.688	166.410	46.886	1.00	57.06	A	C
ATOM	2149	OE1	GLU	A	274	54.777	166.001	47.646	1.00	58.06	A	O
ATOM	2150	OE2	GLU	A	274	55.487	167.211	45.946	1.00	59.62	A	O
ATOM	2151	C	GLU	A	274	59.552	166.285	50.094	1.00	43.12	A	C
ATOM	2152	O	GLU	A	274	59.435	167.465	50.417	1.00	45.78	A	O
ATOM	2153	N	ALA	A	275	60.094	165.372	50.889	1.00	44.15	A	N
ATOM	2154	CA	ALA	A	275	60.610	165.712	52.211	1.00	44.91	A	C
ATOM	2155	CB	ALA	A	275	60.923	164.434	53.001	1.00	41.40	A	C
ATOM	2156	C	ALA	A	275	61.874	166.553	52.024	1.00	47.01	A	C
ATOM	2157	O	ALA	A	275	62.731	166.229	51.208	1.00	47.39	A	O
ATOM	2158	N	PRO	A	276	61.999	167.651	52.780	1.00	51.07	A	N
ATOM	2159	CD	PRO	A	276	61.044	168.115	53.807	1.00	51.78	A	C
ATOM	2160	CA	PRO	A	276	63.161	168.549	52.698	1.00	52.69	A	C
ATOM	2161	CB	PRO	A	276	63.013	169.405	53.950	1.00	53.48	A	C
ATOM	2162	CG	PRO	A	276	61.505	169.540	54.055	1.00	53.72	A	C
ATOM	2163	C	PRO	A	276	64.535	167.874	52.611	1.00	52.70	A	C
ATOM	2164	O	PRO	A	276	65.273	168.083	51.652	1.00	51.45	A	O
ATOM	2165	N	LYS	A	277	64.873	167.055	53.599	1.00	54.12	A	N
ATOM	2166	CA	LYS	A	277	66.177	166.396	53.606	1.00	55.05	A	C
ATOM	2167	CB	LYS	A	277	66.336	165.573	54.882	1.00	57.01	A	C
ATOM	2168	CG	LYS	A	277	66.083	166.326	56.172	1.00	58.78	A	C
ATOM	2169	CD	LYS	A	277	66.701	165.556	57.333	1.00	63.52	A	C
ATOM	2170	CE	LYS	A	277	66.351	166.171	58.681	1.00	66.21	A	C
ATOM	2171	NZ	LYS	A	277	64.887	166.059	58.963	1.00	71.17	A	N
ATOM	2172	C	LYS	A	277	66.483	165.489	52.404	1.00	55.24	A	C
ATOM	2173	O	LYS	A	277	67.608	165.021	52.254	1.00	54.89	A	O
ATOM	2174	N	MET	A	278	65.498	165.240	51.547	1.00	54.10	A	N
ATOM	2175	CA	MET	A	278	65.711	164.354	50.406	1.00	51.32	A	C
ATOM	2176	CB	MET	A	278	64.510	163.417	50.244	1.00	48.90	A	C
ATOM	2177	CG	MET	A	278	64.281	162.483	51.414	1.00	43.08	A	C
ATOM	2178	SD	MET	A	278	65.746	161.469	51.751	1.00	40.62	A	S
ATOM	2179	CE	MET	A	278	65.780	160.478	50.298	1.00	38.00	A	C
ATOM	2180	C	MET	A	278	65.950	165.083	49.091	1.00	52.95	A	C
ATOM	2181	O	MET	A	278	66.058	164.447	48.038	1.00	51.83	A	O
ATOM	2182	N	GLY	A	279	66.026	166.410	49.156	1.00	53.56	A	N
ATOM	2183	CA	GLY	A	279	66.237	167.218	47.963	1.00	53.10	A	C
ATOM	2184	C	GLY	A	279	67.255	166.713	46.948	1.00	53.47	A	C
ATOM	2185	O	GLY	A	279	66.977	166.689	45.747	1.00	53.00	A	O
ATOM	2186	N	ALA	A	280	68.432	166.307	47.418	1.00	53.57	A	N
ATOM	2187	CA	ALA	A	280	69.482	165.819	46.520	1.00	55.19	A	C
ATOM	2188	CB	ALA	A	280	70.855	165.904	47.213	1.00	53.82	A	C
ATOM	2189	C	ALA	A	280	69.241	164.398	46.010	1.00	54.50	A	C
ATOM	2190	O	ALA	A	280	69.789	164.010	44.983	1.00	55.78	A	O
ATOM	2191	N	GLN	A	281	68.422	163.632	46.729	1.00	54.93	A	N
ATOM	2192	CA	GLN	A	281	68.096	162.246	46.360	1.00	53.57	A	C
ATOM	2193	CB	GLN	A	281	68.609	161.287	47.436	1.00	57.35	A	C

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ATOM	2194	CG	GLN	A	281	70.086	160.955	47.365	1.00	61.55	A	C
ATOM	2195	CD	GLN	A	281	70.560	160.259	48.627	1.00	65.43	A	C
ATOM	2196	OE1	GLN	A	281	70.739	160.901	49.666	1.00	68.16	A	O
ATOM	2197	NE2	GLN	A	281	70.741	158.940	48.556	1.00	65.52	A	N
ATOM	2198	C	GLN	A	281	66.584	162.073	46.241	1.00	50.69	A	C
ATOM	2199	O	GLN	A	281	66.006	161.205	46.887	1.00	49.73	A	O
ATOM	2200	N	SER	A	282	65.959	162.893	45.401	1.00	48.87	A	N
ATOM	2201	CA	SER	A	282	64.507	162.902	45.215	1.00	44.40	A	C
ATOM	2202	CB	SER	A	282	64.136	163.927	44.141	1.00	46.84	A	C
ATOM	2203	OG	SER	A	282	64.375	165.248	44.592	1.00	53.81	A	O
ATOM	2204	C	SER	A	282	63.774	161.607	44.901	1.00	40.35	A	C
ATOM	2205	O	SER	A	282	62.813	161.266	45.576	1.00	40.55	A	O
ATOM	2206	N	THR	A	283	64.223	160.910	43.865	1.00	37.18	A	N
ATOM	2207	CA	THR	A	283	63.612	159.678	43.396	1.00	33.97	A	C
ATOM	2208	CB	THR	A	283	64.102	159.374	41.978	1.00	34.43	A	C
ATOM	2209	OG1	THR	A	283	63.879	160.530	41.159	1.00	33.50	A	O
ATOM	2210	CG2	THR	A	283	63.359	158.182	41.393	1.00	31.30	A	C
ATOM	2211	C	THR	A	283	63.847	158.460	44.281	1.00	34.03	A	C
ATOM	2212	O	THR	A	283	64.977	158.023	44.485	1.00	30.78	A	O
ATOM	2213	N	ILE	A	284	62.759	157.891	44.780	1.00	32.03	A	N
ATOM	2214	CA	ILE	A	284	62.879	156.758	45.668	1.00	32.29	A	C
ATOM	2215	CB	ILE	A	284	62.162	157.049	46.976	1.00	34.52	A	C
ATOM	2216	CG2	ILE	A	284	62.818	158.262	47.639	1.00	34.21	A	C
ATOM	2217	CG1	ILE	A	284	60.691	157.345	46.713	1.00	33.87	A	C
ATOM	2218	CD1	ILE	A	284	59.915	157.589	47.969	1.00	38.59	A	C
ATOM	2219	C	ILE	A	284	62.393	155.467	45.067	1.00	30.94	A	C
ATOM	2220	O	ILE	A	284	62.589	154.391	45.634	1.00	32.45	A	O
ATOM	2221	N	CYS	A	285	61.776	155.574	43.903	1.00	28.97	A	N
ATOM	2222	CA	CYS	A	285	61.297	154.413	43.183	1.00	28.31	A	C
ATOM	2223	CB	CYS	A	285	59.930	153.960	43.707	1.00	27.54	A	C
ATOM	2224	SG	CYS	A	285	59.243	152.515	42.835	1.00	29.68	A	S
ATOM	2225	C	CYS	A	285	61.165	154.806	41.726	1.00	29.45	A	C
ATOM	2226	O	CYS	A	285	60.698	155.892	41.418	1.00	29.18	A	O
ATOM	2227	N	ALA	A	286	61.573	153.924	40.827	1.00	29.83	A	N
ATOM	2228	CA	ALA	A	286	61.441	154.226	39.403	1.00	30.78	A	C
ATOM	2229	CB	ALA	A	286	62.677	154.978	38.897	1.00	29.70	A	C
ATOM	2230	C	ALA	A	286	61.205	152.967	38.573	1.00	29.03	A	C
ATOM	2231	O	ALA	A	286	61.628	151.866	38.931	1.00	27.22	A	O
ATOM	2232	N	GLY	A	287	60.484	153.130	37.476	1.00	29.64	A	N
ATOM	2233	CA	GLY	A	287	60.227	151.999	36.616	1.00	30.94	A	C
ATOM	2234	C	GLY	A	287	59.349	152.401	35.457	1.00	33.01	A	C
ATOM	2235	O	GLY	A	287	59.157	153.592	35.182	1.00	33.78	A	O
ATOM	2236	N	GLY	A	288	58.811	151.401	34.774	1.00	31.70	A	N
ATOM	2237	CA	GLY	A	288	57.951	151.674	33.650	1.00	32.18	A	C
ATOM	2238	C	GLY	A	288	57.822	150.443	32.786	1.00	33.34	A	C
ATOM	2239	O	GLY	A	288	58.349	149.377	33.099	1.00	31.07	A	O
ATOM	2240	N	ARG	A	289	57.118	150.603	31.679	1.00	34.27	A	N
ATOM	2241	CA	ARG	A	289	56.898	149.512	30.752	1.00	37.36	A	C
ATOM	2242	CB	ARG	A	289	55.566	149.769	30.042	1.00	37.07	A	C
ATOM	2243	CG	ARG	A	289	55.231	148.837	28.913	1.00	35.61	A	C
ATOM	2244	CD	ARG	A	289	53.801	149.086	28.503	1.00	36.12	A	C
ATOM	2245	NE	ARG	A	289	52.860	148.543	29.475	1.00	33.32	A	N
ATOM	2246	CZ	ARG	A	289	52.751	147.242	29.725	1.00	37.22	A	C
ATOM	2247	NH1	ARG	A	289	53.526	146.379	29.072	1.00	37.55	A	N
ATOM	2248	NH2	ARG	A	289	51.868	146.796	30.609	1.00	36.04	A	N
ATOM	2249	C	ARG	A	289	58.056	149.392	29.753	1.00	38.37	A	C
ATOM	2250	O	ARG	A	289	58.761	150.366	29.470	1.00	37.55	A	O
ATOM	2251	N	TYR	A	290	58.256	148.192	29.229	1.00	41.24	A	N
ATOM	2252	CA	TYR	A	290	59.321	147.958	28.255	1.00	45.89	A	C
ATOM	2253	CB	TYR	A	290	60.668	147.838	28.963	1.00	44.26	A	C
ATOM	2254	CG	TYR	A	290	60.711	146.749	29.998	1.00	44.74	A	C

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ATOM	2255	CD1	TYR	A	290	60.926	145.419	29.633	1.00	45.07	A	C
ATOM	2256	CE1	TYR	A	290	60.937	144.407	30.587	1.00	45.22	A	C
ATOM	2257	CD2	TYR	A	290	60.507	147.041	31.345	1.00	43.37	A	C
ATOM	2258	CE2	TYR	A	290	60.513	146.039	32.306	1.00	45.19	A	C
ATOM	2259	CZ	TYR	A	290	60.729	144.728	31.924	1.00	44.31	A	C
ATOM	2260	OH	TYR	A	290	60.737	143.745	32.875	1.00	44.53	A	O
ATOM	2261	C	TYR	A	290	59.055	146.703	27.437	1.00	48.47	A	C
ATOM	2262	O	TYR	A	290	58.395	145.781	27.910	1.00	49.52	A	O
ATOM	2263	N	ASN	A	291	59.569	146.681	26.208	1.00	53.85	A	N
ATOM	2264	CA	ASN	A	291	59.399	145.548	25.293	1.00	56.71	A	C
ATOM	2265	CB	ASN	A	291	58.325	145.855	24.251	1.00	58.11	A	C
ATOM	2266	CG	ASN	A	291	57.026	146.328	24.860	1.00	62.39	A	C
ATOM	2267	OD1	ASN	A	291	56.163	146.874	24.161	1.00	64.00	A	O
ATOM	2268	ND2	ASN	A	291	56.866	146.112	26.164	1.00	63.32	A	N
ATOM	2269	C	ASN	A	291	60.705	145.299	24.541	1.00	58.91	A	C
ATOM	2270	O	ASN	A	291	60.890	145.815	23.433	1.00	61.45	A	O
ATOM	2271	N	GLY	A	292	61.615	144.527	25.121	1.00	58.40	A	N
ATOM	2272	CA	GLY	A	292	62.852	144.258	24.417	1.00	56.00	A	C
ATOM	2273	C	GLY	A	292	63.893	143.531	25.238	1.00	57.20	A	C
ATOM	2274	O	GLY	A	292	64.760	142.855	24.681	1.00	55.92	A	O
ATOM	2275	N	LEU	A	293	63.816	143.657	26.560	1.00	56.61	A	N
ATOM	2276	CA	LEU	A	293	64.792	143.005	27.423	1.00	57.31	A	C
ATOM	2277	CB	LEU	A	293	64.538	143.353	28.891	1.00	56.72	A	C
ATOM	2278	CG	LEU	A	293	64.467	144.835	29.254	1.00	57.67	A	C
ATOM	2279	CD1	LEU	A	293	64.418	144.957	30.773	1.00	57.84	A	C
ATOM	2280	CD2	LEU	A	293	65.665	145.582	28.696	1.00	58.02	A	C
ATOM	2281	C	LEU	A	293	64.794	141.494	27.270	1.00	56.75	A	C
ATOM	2282	O	LEU	A	293	65.856	140.872	27.239	1.00	56.56	A	O
ATOM	2283	N	VAL	A	294	63.607	140.905	27.181	1.00	57.02	A	N
ATOM	2284	CA	VAL	A	294	63.503	139.461	27.057	1.00	57.51	A	C
ATOM	2285	CB	VAL	A	294	62.045	138.998	27.196	1.00	57.26	A	C
ATOM	2286	CG1	VAL	A	294	61.969	137.479	27.082	1.00	57.60	A	C
ATOM	2287	CG2	VAL	A	294	61.482	139.461	28.535	1.00	56.21	A	C
ATOM	2288	C	VAL	A	294	64.058	139.002	25.717	1.00	59.14	A	C
ATOM	2289	O	VAL	A	294	64.924	138.122	25.662	1.00	58.03	A	O
ATOM	2290	N	GLU	A	295	63.562	139.603	24.640	1.00	60.64	A	N
ATOM	2291	CA	GLU	A	295	64.019	139.259	23.299	1.00	62.59	A	C
ATOM	2292	CB	GLU	A	295	63.312	140.148	22.267	1.00	63.17	A	C
ATOM	2293	CG	GLU	A	295	63.564	139.767	20.812	1.00	65.30	A	C
ATOM	2294	CD	GLU	A	295	62.602	140.453	19.841	1.00	66.63	A	C
ATOM	2295	OE1	GLU	A	295	61.380	140.170	19.905	1.00	65.12	A	O
ATOM	2296	OE2	GLU	A	295	63.071	141.273	19.015	1.00	67.14	A	O
ATOM	2297	C	GLU	A	295	65.535	139.442	23.221	1.00	63.10	A	C
ATOM	2298	O	GLU	A	295	66.253	138.596	22.688	1.00	62.76	A	O
ATOM	2299	N	GLU	A	296	66.013	140.543	23.787	1.00	64.45	A	N
ATOM	2300	CA	GLU	A	296	67.436	140.861	23.790	1.00	66.35	A	C
ATOM	2301	CB	GLU	A	296	67.662	142.203	24.501	1.00	68.28	A	C
ATOM	2302	CG	GLU	A	296	69.022	142.838	24.249	1.00	71.87	A	C
ATOM	2303	CD	GLU	A	296	69.059	144.321	24.609	1.00	74.52	A	C
ATOM	2304	OE1	GLU	A	296	70.107	144.967	24.371	1.00	75.25	A	O
ATOM	2305	OE2	GLU	A	296	68.042	144.842	25.128	1.00	75.67	A	O
ATOM	2306	C	GLU	A	296	68.288	139.774	24.447	1.00	65.77	A	C
ATOM	2307	O	GLU	A	296	69.474	139.645	24.145	1.00	66.88	A	O
ATOM	2308	N	LEU	A	297	67.688	138.995	25.342	1.00	64.16	A	N
ATOM	2309	CA	LEU	A	297	68.419	137.934	26.028	1.00	62.08	A	C
ATOM	2310	CB	LEU	A	297	68.124	137.963	27.529	1.00	62.27	A	C
ATOM	2311	CG	LEU	A	297	69.081	138.811	28.375	1.00	63.39	A	C
ATOM	2312	CD1	LEU	A	297	68.499	139.040	29.757	1.00	61.81	A	C
ATOM	2313	CD2	LEU	A	297	70.431	138.108	28.478	1.00	62.46	A	C
ATOM	2314	C	LEU	A	297	68.124	136.548	25.471	1.00	60.85	A	C
ATOM	2315	O	LEU	A	297	68.410	135.535	26.113	1.00	59.54	A	O

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ATOM	2316	N	GLY	A	298	67.545	136.509	24.276	1.00	59.30	A	N
ATOM	2317	CA	GLY	A	298	67.256	135.235	23.645	1.00	58.34	A	C
ATOM	2318	C	GLY	A	298	65.885	134.637	23.890	1.00	57.62	A	C
ATOM	2319	O	GLY	A	298	65.650	133.479	23.552	1.00	58.40	A	O
ATOM	2320	N	GLY	A	299	64.977	135.409	24.472	1.00	55.94	A	N
ATOM	2321	CA	GLY	A	299	63.648	134.888	24.718	1.00	55.07	A	C
ATOM	2322	C	GLY	A	299	62.656	135.403	23.697	1.00	54.80	A	C
ATOM	2323	O	GLY	A	299	63.036	136.108	22.764	1.00	53.47	A	O
ATOM	2324	N	PRO	A	300	61.369	135.060	23.840	1.00	54.23	A	N
ATOM	2325	CD	PRO	A	300	60.807	134.138	24.838	1.00	52.94	A	C
ATOM	2326	CA	PRO	A	300	60.336	135.515	22.904	1.00	54.41	A	C
ATOM	2327	CB	PRO	A	300	59.118	134.670	23.282	1.00	54.19	A	C
ATOM	2328	CG	PRO	A	300	59.688	133.517	24.072	1.00	54.74	A	C
ATOM	2329	C	PRO	A	300	60.050	137.003	23.116	1.00	55.73	A	C
ATOM	2330	O	PRO	A	300	60.473	137.585	24.116	1.00	56.14	A	O
ATOM	2331	N	ASP	A	301	59.335	137.619	22.179	1.00	56.50	A	N
ATOM	2332	CA	ASP	A	301	58.980	139.024	22.327	1.00	56.43	A	C
ATOM	2333	CB	ASP	A	301	58.275	139.548	21.075	1.00	59.26	A	C
ATOM	2334	CG	ASP	A	301	57.826	140.990	21.225	1.00	63.39	A	C
ATOM	2335	OD1	ASP	A	301	58.697	141.870	21.444	1.00	64.29	A	O
ATOM	2336	OD2	ASP	A	301	56.601	141.241	21.132	1.00	64.94	A	O
ATOM	2337	C	ASP	A	301	58.025	139.046	23.513	1.00	54.19	A	C
ATOM	2338	O	ASP	A	301	56.901	138.538	23.434	1.00	54.13	A	O
ATOM	2339	N	THR	A	302	58.473	139.620	24.620	1.00	50.63	A	N
ATOM	2340	CA	THR	A	302	57.642	139.639	25.813	1.00	47.04	A	C
ATOM	2341	CB	THR	A	302	58.256	138.741	26.903	1.00	46.01	A	C
ATOM	2342	OG1	THR	A	302	58.765	137.550	26.295	1.00	47.15	A	O
ATOM	2343	CG2	THR	A	302	57.211	138.358	27.960	1.00	44.34	A	C
ATOM	2344	C	THR	A	302	57.463	141.034	26.381	1.00	45.07	A	C
ATOM	2345	O	THR	A	302	58.435	141.726	26.673	1.00	45.13	A	O
ATOM	2346	N	PRO	A	303	56.208	141.475	26.524	1.00	44.04	A	N
ATOM	2347	CD	PRO	A	303	54.957	140.852	26.055	1.00	42.41	A	C
ATOM	2348	CA	PRO	A	303	55.956	142.806	27.080	1.00	41.48	A	C
ATOM	2349	CB	PRO	A	303	54.455	143.001	26.862	1.00	42.24	A	C
ATOM	2350	CG	PRO	A	303	54.133	142.066	25.710	1.00	43.10	A	C
ATOM	2351	C	PRO	A	303	56.305	142.706	28.561	1.00	40.29	A	C
ATOM	2352	O	PRO	A	303	56.231	141.624	29.145	1.00	39.22	A	O
ATOM	2353	N	GLY	A	304	56.692	143.822	29.167	1.00	40.13	A	N
ATOM	2354	CA	GLY	A	304	57.049	143.802	30.573	1.00	37.12	A	C
ATOM	2355	C	GLY	A	304	56.903	145.149	31.249	1.00	37.26	A	C
ATOM	2356	O	GLY	A	304	56.808	146.192	30.603	1.00	37.59	A	O
ATOM	2357	N	PHE	A	305	56.864	145.111	32.571	1.00	35.58	A	N
ATOM	2358	CA	PHE	A	305	56.734	146.299	33.381	1.00	33.90	A	C
ATOM	2359	CB	PHE	A	305	55.266	146.604	33.668	1.00	32.20	A	C
ATOM	2360	CG	PHE	A	305	55.019	148.036	34.099	1.00	30.18	A	C
ATOM	2361	CD1	PHE	A	305	54.535	148.966	33.202	1.00	26.73	A	C
ATOM	2362	CD2	PHE	A	305	55.319	148.450	35.397	1.00	29.74	A	C
ATOM	2363	CE1	PHE	A	305	54.356	150.286	33.582	1.00	30.41	A	C
ATOM	2364	CE2	PHE	A	305	55.146	149.763	35.787	1.00	25.82	A	C
ATOM	2365	CZ	PHE	A	305	54.667	150.686	34.883	1.00	30.51	A	C
ATOM	2366	C	PHE	A	305	57.466	145.999	34.683	1.00	35.83	A	C
ATOM	2367	O	PHE	A	305	57.504	144.856	35.143	1.00	34.86	A	O
ATOM	2368	N	GLY	A	306	58.074	147.020	35.266	1.00	34.91	A	N
ATOM	2369	CA	GLY	A	306	58.783	146.793	36.499	1.00	34.53	A	C
ATOM	2370	C	GLY	A	306	59.196	148.100	37.118	1.00	34.39	A	C
ATOM	2371	O	GLY	A	306	58.876	149.181	36.621	1.00	34.00	A	O
ATOM	2372	N	PHE	A	307	59.891	147.992	38.235	1.00	32.55	A	N
ATOM	2373	CA	PHE	A	307	60.397	149.153	38.921	1.00	32.11	A	C
ATOM	2374	CB	PHE	A	307	59.265	149.947	39.630	1.00	32.70	A	C
ATOM	2375	CG	PHE	A	307	58.664	149.262	40.849	1.00	31.91	A	C
ATOM	2376	CD1	PHE	A	307	59.461	148.837	41.913	1.00	31.37	A	C

FIGURE 11-49

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ATOM	2377	CD2	PHE	A	307	57.289	149.103	40.954	1.00	31.03	A	C
ATOM	2378	CE1	PHE	A	307	58.892	148.263	43.067	1.00	32.45	A	C
ATOM	2379	CE2	PHE	A	307	56.711	148.534	42.093	1.00	32.52	A	C
ATOM	2380	CZ	PHE	A	307	57.517	148.112	43.155	1.00	31.91	A	C
ATOM	2381	C	PHE	A	307	61.426	148.663	39.906	1.00	30.77	A	C
ATOM	2382	O	PHE	A	307	61.503	147.479	40.220	1.00	30.80	A	O
ATOM	2383	N	GLY	A	308	62.233	149.580	40.393	1.00	32.67	A	N
ATOM	2384	CA	GLY	A	308	63.230	149.198	41.363	1.00	29.73	A	C
ATOM	2385	C	GLY	A	308	63.340	150.369	42.286	1.00	29.38	A	C
ATOM	2386	O	GLY	A	308	62.965	151.491	41.935	1.00	27.34	A	O
ATOM	2387	N	MET	A	309	63.836	150.098	43.480	1.00	32.08	A	N
ATOM	2388	CA	MET	A	309	64.034	151.129	44.481	1.00	31.75	A	C
ATOM	2389	CB	MET	A	309	62.779	151.252	45.357	1.00	34.53	A	C
ATOM	2390	CG	MET	A	309	62.273	149.936	45.928	1.00	37.28	A	C
ATOM	2391	SD	MET	A	309	60.605	150.066	46.689	1.00	40.85	A	S
ATOM	2392	CE	MET	A	309	59.769	150.962	45.514	1.00	36.90	A	C
ATOM	2393	C	MET	A	309	65.251	150.686	45.293	1.00	29.79	A	C
ATOM	2394	O	MET	A	309	65.481	149.493	45.463	1.00	28.50	A	O
ATOM	2395	N	GLY	A	310	66.061	151.638	45.735	1.00	29.33	A	N
ATOM	2396	CA	GLY	A	310	67.223	151.280	46.523	1.00	28.86	A	C
ATOM	2397	C	GLY	A	310	66.770	151.305	47.965	1.00	29.64	A	C
ATOM	2398	O	GLY	A	310	66.049	152.213	48.368	1.00	30.13	A	O
ATOM	2399	N	ILE	A	311	67.166	150.311	48.744	1.00	30.27	A	N
ATOM	2400	CA	ILE	A	311	66.754	150.266	50.134	1.00	30.93	A	C
ATOM	2401	CB	ILE	A	311	67.040	148.895	50.763	1.00	30.44	A	C
ATOM	2402	CG2	ILE	A	311	66.501	148.863	52.180	1.00	25.75	A	C
ATOM	2403	CG1	ILE	A	311	66.412	147.796	49.904	1.00	27.85	A	C
ATOM	2404	CD1	ILE	A	311	66.253	146.458	50.600	1.00	27.79	A	C
ATOM	2405	C	ILE	A	311	67.446	151.329	50.963	1.00	34.55	A	C
ATOM	2406	O	ILE	A	311	66.845	151.896	51.889	1.00	36.97	A	O
ATOM	2407	N	GLU	A	312	68.714	151.593	50.648	1.00	34.50	A	N
ATOM	2408	CA	GLU	A	312	69.461	152.597	51.385	1.00	33.17	A	C
ATOM	2409	CB	GLU	A	312	70.864	152.781	50.790	1.00	34.30	A	C
ATOM	2410	CG	GLU	A	312	71.869	151.669	51.135	1.00	34.87	A	C
ATOM	2411	CD	GLU	A	312	71.758	150.455	50.236	1.00	34.11	A	C
ATOM	2412	OE1	GLU	A	312	72.576	149.525	50.397	1.00	34.77	A	O
ATOM	2413	OE2	GLU	A	312	70.853	150.421	49.372	1.00	37.49	A	O
ATOM	2414	C	GLU	A	312	68.696	153.914	51.331	1.00	32.66	A	C
ATOM	2415	O	GLU	A	312	68.522	154.578	52.349	1.00	32.96	A	O
ATOM	2416	N	ARG	A	313	68.214	154.273	50.144	1.00	30.75	A	N
ATOM	2417	CA	ARG	A	313	67.481	155.516	49.990	1.00	29.93	A	C
ATOM	2418	CB	ARG	A	313	67.384	155.910	48.521	1.00	33.03	A	C
ATOM	2419	CG	ARG	A	313	66.731	157.265	48.313	1.00	33.35	A	C
ATOM	2420	CD	ARG	A	313	66.897	157.722	46.893	1.00	36.15	A	C
ATOM	2421	NE	ARG	A	313	68.304	157.831	46.524	1.00	39.64	A	N
ATOM	2422	CZ	ARG	A	313	68.732	158.189	45.316	1.00	42.79	A	C
ATOM	2423	NH1	ARG	A	313	67.859	158.473	44.360	1.00	41.24	A	N
ATOM	2424	NH2	ARG	A	313	70.032	158.260	45.059	1.00	42.99	A	N
ATOM	2425	C	ARG	A	313	66.089	155.464	50.601	1.00	29.83	A	C
ATOM	2426	O	ARG	A	313	65.580	156.480	51.042	1.00	33.74	A	O
ATOM	2427	N	VAL	A	314	65.453	154.300	50.611	1.00	29.74	A	N
ATOM	2428	CA	VAL	A	314	64.134	154.192	51.232	1.00	30.28	A	C
ATOM	2429	CB	VAL	A	314	63.527	152.773	51.045	1.00	31.88	A	C
ATOM	2430	CG1	VAL	A	314	62.326	152.579	51.976	1.00	30.34	A	C
ATOM	2431	CG2	VAL	A	314	63.120	152.567	49.587	1.00	28.74	A	C
ATOM	2432	C	VAL	A	314	64.327	154.467	52.731	1.00	27.83	A	C
ATOM	2433	O	VAL	A	314	63.555	155.184	53.350	1.00	28.01	A	O
ATOM	2434	N	LEU	A	315	65.380	153.902	53.303	1.00	31.56	A	N
ATOM	2435	CA	LEU	A	315	65.664	154.094	54.722	1.00	31.02	A	C
ATOM	2436	CB	LEU	A	315	66.840	153.226	55.145	1.00	28.88	A	C
ATOM	2437	CG	LEU	A	315	66.520	151.746	55.282	1.00	27.77	A	C

FIGURE 11-50

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ATOM	2438	CD1	LEU	A	315	67.817	150.962	55.457	1.00	30.64	A	C
ATOM	2439	CD2	LEU	A	315	65.595	151.541	56.470	1.00	26.60	A	C
ATOM	2440	C	LEU	A	315	65.993	155.546	54.982	1.00	32.57	A	C
ATOM	2441	O	LEU	A	315	65.662	156.086	56.033	1.00	32.37	A	O
ATOM	2442	N	LEU	A	316	66.644	156.184	54.016	1.00	34.44	A	N
ATOM	2443	CA	LEU	A	316	67.006	157.582	54.164	1.00	36.10	A	C
ATOM	2444	CB	LEU	A	316	67.889	158.034	53.002	1.00	40.09	A	C
ATOM	2445	CG	LEU	A	316	68.849	159.161	53.377	1.00	45.62	A	C
ATOM	2446	CD1	LEU	A	316	69.998	158.582	54.214	1.00	45.44	A	C
ATOM	2447	CD2	LEU	A	316	69.397	159.825	52.120	1.00	49.23	A	C
ATOM	2448	C	LEU	A	316	65.729	158.412	54.194	1.00	37.36	A	C
ATOM	2449	O	LEU	A	316	65.611	159.364	54.976	1.00	39.28	A	O
ATOM	2450	N	THR	A	317	64.772	158.051	53.341	1.00	35.16	A	N
ATOM	2451	CA	THR	A	317	63.493	158.748	53.289	1.00	34.91	A	C
ATOM	2452	CB	THR	A	317	62.626	158.212	52.161	1.00	36.35	A	C
ATOM	2453	OG1	THR	A	317	63.336	158.327	50.924	1.00	38.69	A	O
ATOM	2454	CG2	THR	A	317	61.334	158.997	52.082	1.00	35.71	A	C
ATOM	2455	C	THR	A	317	62.725	158.556	54.600	1.00	34.27	A	C
ATOM	2456	O	THR	A	317	62.055	159.457	55.083	1.00	35.42	A	O
ATOM	2457	N	MET	A	318	62.805	157.364	55.165	1.00	33.83	A	N
ATOM	2458	CA	MET	A	318	62.123	157.107	56.419	1.00	36.84	A	C
ATOM	2459	CB	MET	A	318	62.274	155.642	56.805	1.00	31.93	A	C
ATOM	2460	CG	MET	A	318	61.442	154.745	55.934	1.00	31.30	A	C
ATOM	2461	SD	MET	A	318	61.585	153.054	56.433	1.00	36.76	A	S
ATOM	2462	CE	MET	A	318	60.544	153.020	57.914	1.00	34.65	A	C
ATOM	2463	C	MET	A	318	62.693	158.022	57.504	1.00	38.07	A	C
ATOM	2464	O	MET	A	318	61.952	158.579	58.313	1.00	37.80	A	O
ATOM	2465	N	GLU	A	319	64.012	158.188	57.487	1.00	38.17	A	N
ATOM	2466	CA	GLU	A	319	64.706	159.042	58.431	1.00	38.25	A	C
ATOM	2467	CB	GLU	A	319	66.216	158.878	58.221	1.00	42.80	A	C
ATOM	2468	CG	GLU	A	319	67.136	159.780	59.019	1.00	49.46	A	C
ATOM	2469	CD	GLU	A	319	68.613	159.467	58.748	1.00	56.72	A	C
ATOM	2470	OE1	GLU	A	319	69.462	160.377	58.902	1.00	60.19	A	O
ATOM	2471	OE2	GLU	A	319	68.931	158.306	58.382	1.00	58.74	A	O
ATOM	2472	C	GLU	A	319	64.263	160.489	58.213	1.00	36.58	A	C
ATOM	2473	O	GLU	A	319	63.900	161.182	59.156	1.00	34.71	A	O
ATOM	2474	N	ALA	A	320	64.267	160.939	56.964	1.00	35.42	A	N
ATOM	2475	CA	ALA	A	320	63.858	162.305	56.664	1.00	33.02	A	C
ATOM	2476	CB	ALA	A	320	63.930	162.546	55.173	1.00	33.83	A	C
ATOM	2477	C	ALA	A	320	62.449	162.615	57.178	1.00	34.03	A	C
ATOM	2478	O	ALA	A	320	62.190	163.704	57.689	1.00	33.77	A	O
ATOM	2479	N	GLU	A	321	61.534	161.666	57.033	1.00	34.30	A	N
ATOM	2480	CA	GLU	A	321	60.159	161.864	57.483	1.00	34.08	A	C
ATOM	2481	CB	GLU	A	321	59.192	161.056	56.613	1.00	33.31	A	C
ATOM	2482	CG	GLU	A	321	59.013	161.630	55.222	1.00	36.38	A	C
ATOM	2483	CD	GLU	A	321	57.783	161.084	54.508	1.00	39.21	A	C
ATOM	2484	OE1	GLU	A	321	56.719	160.927	55.161	1.00	36.21	A	O
ATOM	2485	OE2	GLU	A	321	57.882	160.828	53.288	1.00	40.21	A	O
ATOM	2486	C	GLU	A	321	59.997	161.456	58.932	1.00	35.39	A	C
ATOM	2487	O	GLU	A	321	58.891	161.416	59.462	1.00	34.25	A	O
ATOM	2488	N	GLU	A	322	61.112	161.140	59.570	1.00	38.47	A	N
ATOM	2489	CA	GLU	A	322	61.097	160.729	60.961	1.00	40.60	A	C
ATOM	2490	CB	GLU	A	322	60.845	161.935	61.858	1.00	43.20	A	C
ATOM	2491	CG	GLU	A	322	61.803	163.073	61.562	1.00	49.16	A	C
ATOM	2492	CD	GLU	A	322	61.903	164.054	62.706	1.00	54.05	A	C
ATOM	2493	OE1	GLU	A	322	60.844	164.549	63.161	1.00	53.45	A	O
ATOM	2494	OE2	GLU	A	322	63.047	164.325	63.145	1.00	56.93	A	O
ATOM	2495	C	GLU	A	322	60.055	159.664	61.207	1.00	40.44	A	C
ATOM	2496	O	GLU	A	322	59.207	159.792	62.089	1.00	41.26	A	O
ATOM	2497	N	VAL	A	323	60.123	158.610	60.406	1.00	40.01	A	N
ATOM	2498	CA	VAL	A	323	59.209	157.497	60.535	1.00	41.17	A	C

FIGURE 11-51

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ATOM	2499	CB	VAL	A	323	59.152	156.667	59.260	1.00	38.03	A	C
ATOM	2500	CG1	VAL	A	323	58.202	155.513	59.449	1.00	36.51	A	C
ATOM	2501	CG2	VAL	A	323	58.737	157.531	58.112	1.00	36.44	A	C
ATOM	2502	C	VAL	A	323	59.723	156.591	61.629	1.00	43.20	A	C
ATOM	2503	O	VAL	A	323	60.901	156.247	61.652	1.00	44.81	A	O
ATOM	2504	N	VAL	A	324	58.849	156.199	62.538	1.00	45.82	A	N
ATOM	2505	CA	VAL	A	324	59.284	155.311	63.598	1.00	49.34	A	C
ATOM	2506	CB	VAL	A	324	58.828	155.817	65.004	1.00	52.34	A	C
ATOM	2507	CG1	VAL	A	324	57.305	155.694	65.160	1.00	52.67	A	C
ATOM	2508	CG2	VAL	A	324	59.557	155.043	66.086	1.00	52.68	A	C
ATOM	2509	C	VAL	A	324	58.701	153.938	63.308	1.00	49.76	A	C
ATOM	2510	O	VAL	A	324	57.480	153.753	63.281	1.00	48.00	A	O
ATOM	2511	N	ILE	A	325	59.584	152.984	63.050	1.00	51.51	A	N
ATOM	2512	CA	ILE	A	325	59.157	151.628	62.760	1.00	54.07	A	C
ATOM	2513	CB	ILE	A	325	60.346	150.721	62.391	1.00	53.58	A	C
ATOM	2514	CG2	ILE	A	325	61.246	151.417	61.377	1.00	52.49	A	C
ATOM	2515	CG1	ILE	A	325	61.139	150.387	63.652	1.00	51.64	A	C
ATOM	2516	CD1	ILE	A	325	62.242	149.423	63.427	1.00	55.19	A	C
ATOM	2517	C	ILE	A	325	58.505	151.044	64.008	1.00	55.55	A	C
ATOM	2518	O	ILE	A	325	58.787	151.465	65.125	1.00	53.06	A	O
ATOM	2519	N	PRO	A	326	57.624	150.059	63.823	1.00	59.09	A	N
ATOM	2520	CD	PRO	A	326	57.215	149.507	62.520	1.00	60.93	A	C
ATOM	2521	CA	PRO	A	326	56.921	149.390	64.917	1.00	61.43	A	C
ATOM	2522	CB	PRO	A	326	56.328	148.167	64.236	1.00	60.84	A	C
ATOM	2523	CG	PRO	A	326	55.981	148.702	62.884	1.00	62.11	A	C
ATOM	2524	C	PRO	A	326	57.890	149.012	66.027	1.00	63.93	A	C
ATOM	2525	O	PRO	A	326	58.905	148.351	65.784	1.00	63.73	A	O
ATOM	2526	N	ALA	A	327	57.574	149.442	67.243	1.00	66.36	A	N
ATOM	2527	CA	ALA	A	327	58.408	149.149	68.400	1.00	68.74	A	C
ATOM	2528	CB	ALA	A	327	57.936	149.971	69.595	1.00	68.74	A	C
ATOM	2529	C	ALA	A	327	58.354	147.657	68.732	1.00	70.40	A	C
ATOM	2530	O	ALA	A	327	57.310	147.017	68.573	1.00	69.30	A	O
ATOM	2531	N	LEU	A	328	59.488	147.107	69.173	1.00	73.20	A	N
ATOM	2532	CA	LEU	A	328	59.569	145.698	69.555	1.00	74.59	A	C
ATOM	2533	CB	LEU	A	328	60.931	145.378	70.172	1.00	75.07	A	C
ATOM	2534	CG	LEU	A	328	62.039	144.913	69.229	1.00	76.50	A	C
ATOM	2535	CD1	LEU	A	328	62.163	145.872	68.050	1.00	75.64	A	C
ATOM	2536	CD2	LEU	A	328	63.348	144.812	70.015	1.00	76.08	A	C
ATOM	2537	C	LEU	A	328	58.486	145.420	70.581	1.00	75.82	A	C
ATOM	2538	O	LEU	A	328	58.412	146.084	71.615	1.00	75.99	A	O
ATOM	2539	N	SER	A	329	57.641	144.442	70.291	1.00	77.49	A	N
ATOM	2540	CA	SER	A	329	56.558	144.102	71.196	1.00	78.81	A	C
ATOM	2541	CB	SER	A	329	55.225	144.034	70.438	1.00	80.16	A	C
ATOM	2542	OG	SER	A	329	55.208	142.955	69.517	1.00	80.12	A	O
ATOM	2543	C	SER	A	329	56.849	142.762	71.824	1.00	79.19	A	C
ATOM	2544	O	SER	A	329	56.353	141.736	71.349	1.00	79.27	A	O
ATOM	2545	N	GLU	A	330	57.656	142.759	72.882	1.00	79.27	A	N
ATOM	2546	CA	GLU	A	330	57.974	141.494	73.533	1.00	79.35	A	C
ATOM	2547	CB	GLU	A	330	59.012	140.721	72.704	1.00	80.23	A	C
ATOM	2548	CG	GLU	A	330	60.265	141.511	72.364	1.00	81.64	A	C
ATOM	2549	CD	GLU	A	330	61.532	140.754	72.707	1.00	81.13	A	C
ATOM	2550	OE1	GLU	A	330	61.685	139.606	72.236	1.00	79.13	A	O
ATOM	2551	OE2	GLU	A	330	62.373	141.310	73.447	1.00	81.43	A	O
ATOM	2552	C	GLU	A	330	58.424	141.537	74.988	1.00	77.45	A	C
ATOM	2553	O	GLU	A	330	58.095	142.452	75.746	1.00	77.98	A	O
ATOM	2554	N	LEU	A	331	59.184	140.509	75.348	1.00	76.07	A	N
ATOM	2555	CA	LEU	A	331	59.702	140.297	76.691	1.00	72.65	A	C
ATOM	2556	CB	LEU	A	331	60.637	141.419	77.124	1.00	72.00	A	C
ATOM	2557	CG	LEU	A	331	61.322	140.943	78.410	1.00	73.09	A	C
ATOM	2558	CD1	LEU	A	331	62.036	139.614	78.170	1.00	72.60	A	C
ATOM	2559	CD2	LEU	A	331	62.291	141.979	78.881	1.00	74.70	A	C

FIGURE 11-52

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ATOM	2560	C	LEU	A	331	58.581	140.137	77.709	1.00	69.82	A	C
ATOM	2561	O	LEU	A	331	58.263	141.056	78.471	1.00	69.20	A	O
ATOM	2562	N	ASP	A	332	57.979	138.955	77.701	1.00	67.11	A	N
ATOM	2563	CA	ASP	A	332	56.900	138.640	78.619	1.00	64.40	A	C
ATOM	2564	CB	ASP	A	332	56.233	137.323	78.220	1.00	65.68	A	C
ATOM	2565	CG	ASP	A	332	55.517	137.413	76.889	1.00	67.52	A	C
ATOM	2566	OD1	ASP	A	332	54.654	138.302	76.745	1.00	69.59	A	O
ATOM	2567	OD2	ASP	A	332	55.809	136.594	75.990	1.00	68.66	A	O
ATOM	2568	C	ASP	A	332	57.465	138.509	80.020	1.00	62.06	A	C
ATOM	2569	O	ASP	A	332	56.801	138.840	81.008	1.00	61.93	A	O
ATOM	2570	N	ALA	A	333	58.702	138.037	80.109	1.00	58.87	A	N
ATOM	2571	CA	ALA	A	333	59.307	137.855	81.414	1.00	57.13	A	C
ATOM	2572	CB	ALA	A	333	58.757	136.576	82.063	1.00	56.82	A	C
ATOM	2573	C	ALA	A	333	60.823	137.820	81.426	1.00	54.66	A	C
ATOM	2574	O	ALA	A	333	61.476	137.442	80.450	1.00	53.18	A	O
ATOM	2575	N	TYR	A	334	61.367	138.218	82.568	1.00	51.72	A	N
ATOM	2576	CA	TYR	A	334	62.796	138.232	82.780	1.00	49.75	A	C
ATOM	2577	CB	TYR	A	334	63.306	139.663	82.932	1.00	47.65	A	C
ATOM	2578	CG	TYR	A	334	64.798	139.741	82.797	1.00	48.54	A	C
ATOM	2579	CD1	TYR	A	334	65.402	139.844	81.540	1.00	46.57	A	C
ATOM	2580	CE1	TYR	A	334	66.792	139.844	81.407	1.00	47.38	A	C
ATOM	2581	CD2	TYR	A	334	65.618	139.640	83.919	1.00	48.41	A	C
ATOM	2582	CE2	TYR	A	334	67.003	139.636	83.802	1.00	49.97	A	C
ATOM	2583	CZ	TYR	A	334	67.586	139.738	82.546	1.00	50.17	A	C
ATOM	2584	OH	TYR	A	334	68.962	139.732	82.448	1.00	52.56	A	O
ATOM	2585	C	TYR	A	334	63.062	137.463	84.062	1.00	48.97	A	C
ATOM	2586	O	TYR	A	334	62.512	137.781	85.114	1.00	49.89	A	O
ATOM	2587	N	VAL	A	335	63.908	136.448	83.975	1.00	48.76	A	N
ATOM	2588	CA	VAL	A	335	64.234	135.637	85.135	1.00	46.66	A	C
ATOM	2589	CB	VAL	A	335	64.361	134.163	84.729	1.00	44.49	A	C
ATOM	2590	CG1	VAL	A	335	64.650	133.304	85.948	1.00	45.61	A	C
ATOM	2591	CG2	VAL	A	335	63.081	133.714	84.039	1.00	38.67	A	C
ATOM	2592	C	VAL	A	335	65.525	136.104	85.816	1.00	48.02	A	C
ATOM	2593	O	VAL	A	335	66.618	135.993	85.263	1.00	50.07	A	O
ATOM	2594	N	VAL	A	336	65.379	136.641	87.021	1.00	48.52	A	N
ATOM	2595	CA	VAL	A	336	66.507	137.122	87.800	1.00	48.28	A	C
ATOM	2596	CB	VAL	A	336	66.117	138.361	88.610	1.00	47.72	A	C
ATOM	2597	CG1	VAL	A	336	67.234	138.731	89.567	1.00	46.98	A	C
ATOM	2598	CG2	VAL	A	336	65.810	139.513	87.670	1.00	46.73	A	C
ATOM	2599	C	VAL	A	336	66.981	136.038	88.763	1.00	50.86	A	C
ATOM	2600	O	VAL	A	336	66.224	135.573	89.619	1.00	52.30	A	O
ATOM	2601	N	GLY	A	337	68.235	135.631	88.609	1.00	51.74	A	N
ATOM	2602	CA	GLY	A	337	68.791	134.614	89.477	1.00	52.95	A	C
ATOM	2603	C	GLY	A	337	69.846	135.212	90.385	1.00	54.70	A	C
ATOM	2604	O	GLY	A	337	70.870	135.699	89.905	1.00	54.43	A	O
ATOM	2605	N	ILE	A	338	69.598	135.187	91.692	1.00	56.43	A	N
ATOM	2606	CA	ILE	A	338	70.542	135.734	92.655	1.00	58.58	A	C
ATOM	2607	CB	ILE	A	338	69.818	136.467	93.796	1.00	59.10	A	C
ATOM	2608	CG2	ILE	A	338	70.828	137.282	94.598	1.00	58.37	A	C
ATOM	2609	CG1	ILE	A	338	68.734	137.386	93.227	1.00	59.14	A	C
ATOM	2610	CD1	ILE	A	338	67.986	138.186	94.290	1.00	57.57	A	C
ATOM	2611	C	ILE	A	338	71.398	134.628	93.262	1.00	59.93	A	C
ATOM	2612	O	ILE	A	338	70.923	133.839	94.076	1.00	61.42	A	O
ATOM	2613	N	GLY	A	339	72.664	134.571	92.865	1.00	61.13	A	N
ATOM	2614	CA	GLY	A	339	73.548	133.546	93.389	1.00	62.48	A	C
ATOM	2615	C	GLY	A	339	73.925	132.476	92.378	1.00	62.93	A	C
ATOM	2616	O	GLY	A	339	73.067	131.872	91.742	1.00	62.69	A	O
ATOM	2617	N	SER	A	340	75.225	132.240	92.249	1.00	63.32	A	N
ATOM	2618	CA	SER	A	340	75.765	131.256	91.323	1.00	64.75	A	C
ATOM	2619	CB	SER	A	340	77.217	130.930	91.699	1.00	66.19	A	C
ATOM	2620	OG	SER	A	340	77.963	132.112	91.961	1.00	69.15	A	O

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ATOM	2621	C	SER	A	340	74.969	129.954	91.264	1.00	64.69	A	C
ATOM	2622	O	SER	A	340	74.736	129.416	90.182	1.00	64.46	A	O
ATOM	2623	N	ASP	A	341	74.555	129.443	92.420	1.00	64.70	A	N
ATOM	2624	CA	ASP	A	341	73.819	128.181	92.462	1.00	63.69	A	C
ATOM	2625	CB	ASP	A	341	73.771	127.642	93.894	1.00	67.31	A	C
ATOM	2626	CG	ASP	A	341	75.139	127.234	94.406	1.00	70.14	A	C
ATOM	2627	OD1	ASP	A	341	75.926	128.133	94.779	1.00	72.20	A	O
ATOM	2628	OD2	ASP	A	341	75.431	126.014	94.420	1.00	70.95	A	O
ATOM	2629	C	ASP	A	341	72.412	128.247	91.898	1.00	61.00	A	C
ATOM	2630	O	ASP	A	341	71.700	127.251	91.851	1.00	60.31	A	O
ATOM	2631	N	THR	A	342	72.018	129.424	91.447	1.00	59.71	A	N
ATOM	2632	CA	THR	A	342	70.688	129.611	90.899	1.00	58.26	A	C
ATOM	2633	CB	THR	A	342	70.162	130.995	91.351	1.00	59.30	A	C
ATOM	2634	OG1	THR	A	342	68.763	130.909	91.649	1.00	64.24	A	O
ATOM	2635	CG2	THR	A	342	70.406	132.037	90.288	1.00	59.08	A	C
ATOM	2636	C	THR	A	342	70.732	129.487	89.360	1.00	56.86	A	C
ATOM	2637	O	THR	A	342	69.703	129.511	88.677	1.00	54.13	A	O
ATOM	2638	N	ASN	A	343	71.945	129.314	88.840	1.00	55.31	A	N
ATOM	2639	CA	ASN	A	343	72.204	129.216	87.410	1.00	53.54	A	C
ATOM	2640	CB	ASN	A	343	73.671	128.845	87.185	1.00	52.30	A	C
ATOM	2641	CG	ASN	A	343	74.164	129.236	85.809	1.00	52.09	A	C
ATOM	2642	OD1	ASN	A	343	73.798	130.289	85.290	1.00	52.28	A	O
ATOM	2643	ND2	ASN	A	343	75.017	128.403	85.219	1.00	50.14	A	N
ATOM	2644	C	ASN	A	343	71.310	128.231	86.679	1.00	53.47	A	C
ATOM	2645	O	ASN	A	343	70.569	128.608	85.774	1.00	54.07	A	O
ATOM	2646	N	VAL	A	344	71.385	126.966	87.074	1.00	52.53	A	N
ATOM	2647	CA	VAL	A	344	70.591	125.920	86.447	1.00	49.67	A	C
ATOM	2648	CB	VAL	A	344	70.822	124.566	87.134	1.00	49.15	A	C
ATOM	2649	CG1	VAL	A	344	70.064	123.479	86.403	1.00	48.68	A	C
ATOM	2650	CG2	VAL	A	344	72.302	124.249	87.152	1.00	49.59	A	C
ATOM	2651	C	VAL	A	344	69.098	126.217	86.449	1.00	48.48	A	C
ATOM	2652	O	VAL	A	344	68.455	126.165	85.404	1.00	48.01	A	O
ATOM	2653	N	ALA	A	345	68.544	126.520	87.618	1.00	46.52	A	N
ATOM	2654	CA	ALA	A	345	67.119	126.808	87.718	1.00	46.04	A	C
ATOM	2655	CB	ALA	A	345	66.738	127.106	89.169	1.00	46.34	A	C
ATOM	2656	C	ALA	A	345	66.735	127.979	86.825	1.00	45.48	A	C
ATOM	2657	O	ALA	A	345	65.667	127.977	86.207	1.00	44.50	A	O
ATOM	2658	N	ALA	A	346	67.611	128.981	86.765	1.00	46.08	A	N
ATOM	2659	CA	ALA	A	346	67.374	130.162	85.941	1.00	45.01	A	C
ATOM	2660	CB	ALA	A	346	68.561	131.105	86.031	1.00	46.09	A	C
ATOM	2661	C	ALA	A	346	67.139	129.746	84.487	1.00	45.32	A	C
ATOM	2662	O	ALA	A	346	66.221	130.243	83.832	1.00	46.54	A	O
ATOM	2663	N	LEU	A	347	67.972	128.838	83.988	1.00	44.22	A	N
ATOM	2664	CA	LEU	A	347	67.831	128.345	82.626	1.00	44.28	A	C
ATOM	2665	CB	LEU	A	347	69.026	127.469	82.255	1.00	41.69	A	C
ATOM	2666	CG	LEU	A	347	68.927	126.833	80.866	1.00	41.33	A	C
ATOM	2667	CD1	LEU	A	347	69.098	127.915	79.805	1.00	41.15	A	C
ATOM	2668	CD2	LEU	A	347	69.991	125.784	80.692	1.00	38.06	A	C
ATOM	2669	C	LEU	A	347	66.544	127.518	82.483	1.00	46.87	A	C
ATOM	2670	O	LEU	A	347	65.812	127.657	81.497	1.00	47.27	A	O
ATOM	2671	N	GLN	A	348	66.265	126.660	83.464	1.00	46.53	A	N
ATOM	2672	CA	GLN	A	348	65.071	125.820	83.397	1.00	49.09	A	C
ATOM	2673	CB	GLN	A	348	64.956	124.918	84.630	1.00	51.30	A	C
ATOM	2674	CG	GLN	A	348	66.225	124.177	84.990	1.00	56.51	A	C
ATOM	2675	CD	GLN	A	348	66.006	123.150	86.084	1.00	56.11	A	C
ATOM	2676	OE1	GLN	A	348	65.276	122.180	85.895	1.00	59.37	A	O
ATOM	2677	NE2	GLN	A	348	66.637	123.360	87.234	1.00	57.24	A	N
ATOM	2678	C	GLN	A	348	63.851	126.716	83.333	1.00	47.37	A	C
ATOM	2679	O	GLN	A	348	62.910	126.469	82.578	1.00	46.14	A	O
ATOM	2680	N	LEU	A	349	63.889	127.762	84.141	1.00	46.11	A	N
ATOM	2681	CA	LEU	A	349	62.803	128.722	84.221	1.00	48.09	A	C

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ATOM	2682	CB	LEU	A	349	63.116	129.719	85.341	1.00	48.35	A	C
ATOM	2683	CG	LEU	A	349	62.107	130.003	86.460	1.00	47.66	A	C
ATOM	2684	CD1	LEU	A	349	61.315	128.757	86.813	1.00	44.02	A	C
ATOM	2685	CD2	LEU	A	349	62.873	130.539	87.676	1.00	45.02	A	C
ATOM	2686	C	LEU	A	349	62.558	129.455	82.889	1.00	48.67	A	C
ATOM	2687	O	LEU	A	349	61.417	129.534	82.427	1.00	47.19	A	O
ATOM	2688	N	VAL	A	350	63.618	129.972	82.266	1.00	47.89	A	N
ATOM	2689	CA	VAL	A	350	63.451	130.691	81.009	1.00	48.32	A	C
ATOM	2690	CB	VAL	A	350	64.731	131.476	80.598	1.00	49.72	A	C
ATOM	2691	CG1	VAL	A	350	65.852	130.526	80.209	1.00	48.81	A	C
ATOM	2692	CG2	VAL	A	350	64.415	132.386	79.436	1.00	51.58	A	C
ATOM	2693	C	VAL	A	350	63.051	129.771	79.870	1.00	49.16	A	C
ATOM	2694	O	VAL	A	350	62.298	130.173	78.987	1.00	48.96	A	O
ATOM	2695	N	GLN	A	351	63.536	128.535	79.869	1.00	49.45	A	N
ATOM	2696	CA	GLN	A	351	63.149	127.635	78.789	1.00	51.84	A	C
ATOM	2697	CB	GLN	A	351	64.042	126.389	78.746	1.00	50.72	A	C
ATOM	2698	CG	GLN	A	351	65.402	126.656	78.116	1.00	49.94	A	C
ATOM	2699	CD	GLN	A	351	65.290	127.496	76.845	1.00	49.54	A	C
ATOM	2700	OE1	GLN	A	351	64.691	127.076	75.849	1.00	47.25	A	O
ATOM	2701	NE2	GLN	A	351	65.855	128.697	76.885	1.00	47.61	A	N
ATOM	2702	C	GLN	A	351	61.682	127.235	78.905	1.00	53.61	A	C
ATOM	2703	O	GLN	A	351	60.978	127.153	77.898	1.00	56.84	A	O
ATOM	2704	N	SER	A	352	61.219	126.996	80.129	1.00	53.40	A	N
ATOM	2705	CA	SER	A	352	59.827	126.628	80.349	1.00	53.23	A	C
ATOM	2706	CB	SER	A	352	59.569	126.347	81.833	1.00	54.40	A	C
ATOM	2707	OG	SER	A	352	60.073	125.072	82.202	1.00	57.62	A	O
ATOM	2708	C	SER	A	352	58.919	127.751	79.872	1.00	52.89	A	C
ATOM	2709	O	SER	A	352	57.911	127.502	79.214	1.00	53.27	A	O
ATOM	2710	N	ILE	A	353	59.278	128.988	80.206	1.00	53.02	A	N
ATOM	2711	CA	ILE	A	353	58.489	130.140	79.789	1.00	53.10	A	C
ATOM	2712	CB	ILE	A	353	59.078	131.461	80.342	1.00	50.86	A	C
ATOM	2713	CG2	ILE	A	353	58.346	132.655	79.746	1.00	49.42	A	C
ATOM	2714	CG1	ILE	A	353	58.956	131.478	81.868	1.00	50.88	A	C
ATOM	2715	CD1	ILE	A	353	59.528	132.716	82.536	1.00	46.87	A	C
ATOM	2716	C	ILE	A	353	58.454	130.181	78.262	1.00	54.12	A	C
ATOM	2717	O	ILE	A	353	57.405	130.418	77.660	1.00	54.39	A	O
ATOM	2718	N	ARG	A	354	59.599	129.935	77.635	1.00	54.49	A	N
ATOM	2719	CA	ARG	A	354	59.658	129.929	76.182	1.00	54.62	A	C
ATOM	2720	CB	ARG	A	354	61.108	129.851	75.711	1.00	52.11	A	C
ATOM	2721	CG	ARG	A	354	61.865	131.162	75.881	1.00	50.93	A	C
ATOM	2722	CD	ARG	A	354	63.352	130.993	75.664	1.00	45.70	A	C
ATOM	2723	NE	ARG	A	354	64.069	132.252	75.827	1.00	46.40	A	N
ATOM	2724	CZ	ARG	A	354	65.378	132.342	76.053	1.00	45.16	A	C
ATOM	2725	NH1	ARG	A	354	66.116	131.246	76.154	1.00	42.38	A	N
ATOM	2726	NH2	ARG	A	354	65.960	133.529	76.153	1.00	45.77	A	N
ATOM	2727	C	ARG	A	354	58.867	128.740	75.658	1.00	56.76	A	C
ATOM	2728	O	ARG	A	354	58.335	128.777	74.552	1.00	56.97	A	O
ATOM	2729	N	ASN	A	355	58.780	127.688	76.464	1.00	59.07	A	N
ATOM	2730	CA	ASN	A	355	58.043	126.497	76.071	1.00	61.26	A	C
ATOM	2731	CB	ASN	A	355	58.329	125.345	77.034	1.00	64.80	A	C
ATOM	2732	CG	ASN	A	355	57.842	124.008	76.495	1.00	69.75	A	C
ATOM	2733	OD1	ASN	A	355	58.341	123.527	75.472	1.00	72.24	A	O
ATOM	2734	ND2	ASN	A	355	56.859	123.406	77.171	1.00	68.76	A	N
ATOM	2735	C	ASN	A	355	56.535	126.761	76.030	1.00	61.29	A	C
ATOM	2736	O	ASN	A	355	55.796	126.079	75.316	1.00	60.42	A	O
ATOM	2737	N	PHE	A	356	56.078	127.740	76.804	1.00	60.98	A	N
ATOM	2738	CA	PHE	A	356	54.662	128.080	76.821	1.00	62.03	A	C
ATOM	2739	CB	PHE	A	356	54.212	128.492	78.228	1.00	63.50	A	C
ATOM	2740	CG	PHE	A	356	53.920	127.329	79.133	1.00	65.74	A	C
ATOM	2741	CD1	PHE	A	356	54.952	126.533	79.626	1.00	66.97	A	C
ATOM	2742	CD2	PHE	A	356	52.609	127.001	79.460	1.00	67.13	A	C

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ATOM	2743	CE1	PHE	A	356	54.682	125.423	80.430	1.00	66.68	A	C
ATOM	2744	CE2	PHE	A	356	52.325	125.894	80.263	1.00	67.26	A	C
ATOM	2745	CZ	PHE	A	356	53.364	125.104	80.748	1.00	67.64	A	C
ATOM	2746	C	PHE	A	356	54.345	129.195	75.831	1.00	62.74	A	C
ATOM	2747	O	PHE	A	356	53.339	129.897	75.979	1.00	64.04	A	O
ATOM	2748	N	GLY	A	357	55.211	129.363	74.833	1.00	61.84	A	N
ATOM	2749	CA	GLY	A	357	54.993	130.380	73.815	1.00	60.87	A	C
ATOM	2750	C	GLY	A	357	55.451	131.800	74.117	1.00	60.25	A	C
ATOM	2751	O	GLY	A	357	55.687	132.585	73.193	1.00	60.47	A	O
ATOM	2752	N	PHE	A	358	55.584	132.139	75.396	1.00	57.84	A	N
ATOM	2753	CA	PHE	A	358	56.009	133.476	75.789	1.00	55.46	A	C
ATOM	2754	CB	PHE	A	358	55.727	133.686	77.267	1.00	56.07	A	C
ATOM	2755	CG	PHE	A	358	54.307	133.410	77.656	1.00	56.93	A	C
ATOM	2756	CD1	PHE	A	358	53.895	132.119	77.962	1.00	56.76	A	C
ATOM	2757	CD2	PHE	A	358	53.381	134.449	77.734	1.00	58.48	A	C
ATOM	2758	CE1	PHE	A	358	52.579	131.863	78.348	1.00	58.47	A	C
ATOM	2759	CE2	PHE	A	358	52.061	134.204	78.117	1.00	58.87	A	C
ATOM	2760	CZ	PHE	A	358	51.661	132.911	78.425	1.00	57.49	A	C
ATOM	2761	C	PHE	A	358	57.483	133.786	75.504	1.00	53.58	A	C
ATOM	2762	O	PHE	A	358	58.253	132.912	75.118	1.00	54.47	A	O
ATOM	2763	N	SER	A	359	57.860	135.049	75.685	1.00	51.32	A	N
ATOM	2764	CA	SER	A	359	59.233	135.489	75.458	1.00	48.53	A	C
ATOM	2765	CB	SER	A	359	59.249	136.804	74.687	1.00	48.54	A	C
ATOM	2766	OG	SER	A	359	58.700	137.844	75.481	1.00	49.78	A	O
ATOM	2767	C	SER	A	359	59.922	135.696	76.803	1.00	46.80	A	C
ATOM	2768	O	SER	A	359	59.305	136.161	77.767	1.00	44.80	A	O
ATOM	2769	N	ALA	A	360	61.207	135.375	76.862	1.00	45.26	A	N
ATOM	2770	CA	ALA	A	360	61.933	135.519	78.107	1.00	45.01	A	C
ATOM	2771	CB	ALA	A	360	61.694	134.287	78.978	1.00	44.59	A	C
ATOM	2772	C	ALA	A	360	63.426	135.732	77.937	1.00	44.26	A	C
ATOM	2773	O	ALA	A	360	63.997	135.506	76.867	1.00	42.40	A	O
ATOM	2774	N	ASP	A	361	64.048	136.167	79.023	1.00	42.32	A	N
ATOM	2775	CA	ASP	A	361	65.479	136.380	79.052	1.00	41.91	A	C
ATOM	2776	CB	ASP	A	361	65.842	137.755	78.474	1.00	42.19	A	C
ATOM	2777	CG	ASP	A	361	67.322	137.866	78.104	1.00	45.99	A	C
ATOM	2778	OD1	ASP	A	361	67.805	139.005	77.916	1.00	50.55	A	O
ATOM	2779	OD2	ASP	A	361	68.001	136.815	77.990	1.00	46.77	A	O
ATOM	2780	C	ASP	A	361	65.953	136.282	80.502	1.00	40.26	A	C
ATOM	2781	O	ASP	A	361	65.161	136.361	81.446	1.00	39.14	A	O
ATOM	2782	N	ARG	A	362	67.254	136.104	80.665	1.00	40.29	A	N
ATOM	2783	CA	ARG	A	362	67.851	136.013	81.980	1.00	39.94	A	C
ATOM	2784	CB	ARG	A	362	67.846	134.565	82.459	1.00	38.50	A	C
ATOM	2785	CG	ARG	A	362	68.506	133.610	81.489	1.00	40.47	A	C
ATOM	2786	CD	ARG	A	362	69.051	132.384	82.201	1.00	42.43	A	C
ATOM	2787	NE	ARG	A	362	70.098	132.739	83.167	1.00	42.07	A	N
ATOM	2788	CZ	ARG	A	362	70.918	131.854	83.726	1.00	39.97	A	C
ATOM	2789	NH1	ARG	A	362	70.811	130.570	83.419	1.00	39.00	A	N
ATOM	2790	NH2	ARG	A	362	71.852	132.249	84.574	1.00	37.17	A	N
ATOM	2791	C	ARG	A	362	69.284	136.502	81.853	1.00	41.80	A	C
ATOM	2792	O	ARG	A	362	69.779	136.715	80.736	1.00	42.18	A	O
ATOM	2793	N	ASP	A	363	69.948	136.681	82.990	1.00	39.74	A	N
ATOM	2794	CA	ASP	A	363	71.330	137.114	82.979	1.00	39.41	A	C
ATOM	2795	CB	ASP	A	363	71.668	137.848	84.271	1.00	40.75	A	C
ATOM	2796	CG	ASP	A	363	72.883	138.725	84.119	1.00	44.48	A	C
ATOM	2797	OD1	ASP	A	363	74.014	138.251	84.354	1.00	39.07	A	O
ATOM	2798	OD2	ASP	A	363	72.695	139.897	83.719	1.00	52.59	A	O
ATOM	2799	C	ASP	A	363	72.257	135.906	82.782	1.00	39.92	A	C
ATOM	2800	O	ASP	A	363	71.904	134.775	83.114	1.00	40.49	A	O
ATOM	2801	N	TYR	A	364	73.428	136.146	82.203	1.00	39.89	A	N
ATOM	2802	CA	TYR	A	364	74.386	135.082	81.940	1.00	41.28	A	C
ATOM	2803	CB	TYR	A	364	74.371	134.701	80.457	1.00	39.18	A	C

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ATOM	2804	CG	TYR	A	364	73.197	133.835	80.075	1.00	40.90	A	C
ATOM	2805	CD1	TYR	A	364	72.250	134.269	79.146	1.00	39.62	A	C
ATOM	2806	CE1	TYR	A	364	71.162	133.471	78.805	1.00	39.88	A	C
ATOM	2807	CD2	TYR	A	364	73.026	132.581	80.655	1.00	38.81	A	C
ATOM	2808	CE2	TYR	A	364	71.950	131.780	80.325	1.00	41.50	A	C
ATOM	2809	CZ	TYR	A	364	71.017	132.221	79.400	1.00	41.93	A	C
ATOM	2810	OH	TYR	A	364	69.960	131.394	79.069	1.00	38.31	A	O
ATOM	2811	C	TYR	A	364	75.781	135.520	82.329	1.00	42.38	A	C
ATOM	2812	O	TYR	A	364	76.741	134.769	82.174	1.00	40.90	A	O
ATOM	2813	N	MET	A	365	75.869	136.743	82.841	1.00	44.68	A	N
ATOM	2814	CA	MET	A	365	77.132	137.343	83.255	1.00	47.83	A	C
ATOM	2815	CB	MET	A	365	77.190	138.791	82.763	1.00	45.49	A	C
ATOM	2816	CG	MET	A	365	76.994	138.930	81.270	1.00	42.57	A	C
ATOM	2817	SD	MET	A	365	78.204	137.929	80.383	1.00	46.39	A	S
ATOM	2818	CE	MET	A	365	79.725	138.748	80.918	1.00	42.26	A	C
ATOM	2819	C	MET	A	365	77.295	137.311	84.775	1.00	51.27	A	C
ATOM	2820	O	MET	A	365	78.203	137.945	85.317	1.00	51.91	A	O
ATOM	2821	N	ASN	A	366	76.403	136.578	85.444	1.00	53.99	A	N
ATOM	2822	CA	ASN	A	366	76.410	136.434	86.899	1.00	56.62	A	C
ATOM	2823	CB	ASN	A	366	77.518	135.452	87.323	1.00	59.67	A	C
ATOM	2824	CG	ASN	A	366	77.403	135.018	88.785	1.00	61.76	A	C
ATOM	2825	OD1	ASN	A	366	76.302	134.849	89.318	1.00	62.56	A	O
ATOM	2826	ND2	ASN	A	366	78.545	134.818	89.431	1.00	62.93	A	N
ATOM	2827	C	ASN	A	366	76.599	137.788	87.568	1.00	57.41	A	C
ATOM	2828	O	ASN	A	366	77.516	137.988	88.361	1.00	56.53	A	O
ATOM	2829	N	ARG	A	367	75.710	138.718	87.240	1.00	58.89	A	N
ATOM	2830	CA	ARG	A	367	75.771	140.065	87.786	1.00	60.20	A	C
ATOM	2831	CB	ARG	A	367	75.333	141.075	86.722	1.00	61.20	A	C
ATOM	2832	CG	ARG	A	367	76.150	140.981	85.444	1.00	63.43	A	C
ATOM	2833	CD	ARG	A	367	75.747	142.038	84.445	1.00	65.17	A	C
ATOM	2834	NE	ARG	A	367	74.299	142.090	84.305	1.00	69.75	A	N
ATOM	2835	CZ	ARG	A	367	73.663	142.716	83.321	1.00	72.12	A	C
ATOM	2836	NH1	ARG	A	367	72.333	142.708	83.284	1.00	70.94	A	N
ATOM	2837	NH2	ARG	A	367	74.357	143.336	82.369	1.00	73.82	A	N
ATOM	2838	C	ARG	A	367	74.907	140.214	89.023	1.00	60.31	A	C
ATOM	2839	O	ARG	A	367	74.043	139.376	89.290	1.00	59.81	A	O
ATOM	2840	N	LYS	A	368	75.143	141.287	89.774	1.00	61.22	A	N
ATOM	2841	CA	LYS	A	368	74.376	141.547	90.987	1.00	62.16	A	C
ATOM	2842	CB	LYS	A	368	74.926	142.768	91.725	1.00	61.01	A	C
ATOM	2843	CG	LYS	A	368	76.292	142.553	92.350	1.00	59.96	A	C
ATOM	2844	CD	LYS	A	368	76.612	143.703	93.291	1.00	61.23	A	C
ATOM	2845	CE	LYS	A	368	78.018	143.593	93.869	1.00	60.24	A	C
ATOM	2846	NZ	LYS	A	368	78.275	144.703	94.836	1.00	59.17	A	N
ATOM	2847	C	LYS	A	368	72.901	141.759	90.675	1.00	62.59	A	C
ATOM	2848	O	LYS	A	368	72.544	142.273	89.616	1.00	63.08	A	O
ATOM	2849	N	PRO	A	369	72.023	141.366	91.607	1.00	63.32	A	N
ATOM	2850	CD	PRO	A	369	72.355	140.896	92.962	1.00	62.99	A	C
ATOM	2851	CA	PRO	A	369	70.571	141.503	91.441	1.00	63.56	A	C
ATOM	2852	CB	PRO	A	369	70.023	141.107	92.816	1.00	63.57	A	C
ATOM	2853	CG	PRO	A	369	71.175	141.391	93.750	1.00	64.55	A	C
ATOM	2854	C	PRO	A	369	70.109	142.886	90.990	1.00	63.51	A	C
ATOM	2855	O	PRO	A	369	69.227	143.005	90.135	1.00	63.90	A	O
ATOM	2856	N	LYS	A	370	70.707	143.926	91.560	1.00	63.51	A	N
ATOM	2857	CA	LYS	A	370	70.363	145.302	91.202	1.00	63.84	A	C
ATOM	2858	CB	LYS	A	370	71.261	146.278	91.982	1.00	65.59	A	C
ATOM	2859	CG	LYS	A	370	70.992	147.764	91.724	1.00	68.21	A	C
ATOM	2860	CD	LYS	A	370	69.597	148.182	92.178	1.00	69.71	A	C
ATOM	2861	CE	LYS	A	370	69.363	149.690	92.013	1.00	70.99	A	C
ATOM	2862	NZ	LYS	A	370	70.121	150.523	93.000	1.00	71.57	A	N
ATOM	2863	C	LYS	A	370	70.531	145.526	89.690	1.00	61.80	A	C
ATOM	2864	O	LYS	A	370	69.669	146.116	89.037	1.00	61.70	A	O

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ATOM	2865	N	ALA A 371	71.641	145.047	89.140	1.00	59.20	A	N
ATOM	2866	CA	ALA A 371	71.910	145.202	87.717	1.00	58.19	A	C
ATOM	2867	CB	ALA A 371	73.315	144.722	87.401	1.00	55.80	A	C
ATOM	2868	C	ALA A 371	70.897	144.442	86.868	1.00	57.61	A	C
ATOM	2869	O	ALA A 371	70.444	144.937	85.832	1.00	58.05	A	O
ATOM	2870	N	GLN A 372	70.546	143.236	87.302	1.00	56.44	A	N
ATOM	2871	CA	GLN A 372	69.587	142.428	86.566	1.00	55.83	A	C
ATOM	2872	CB	GLN A 372	69.458	141.045	87.192	1.00	56.05	A	C
ATOM	2873	CG	GLN A 372	70.726	140.228	87.142	1.00	56.62	A	C
ATOM	2874	CD	GLN A 372	70.519	138.820	87.655	1.00	58.80	A	C
ATOM	2875	OE1	GLN A 372	69.673	138.073	87.144	1.00	57.69	A	O
ATOM	2876	NE2	GLN A 372	71.291	138.444	88.671	1.00	59.51	A	N
ATOM	2877	C	GLN A 372	68.216	143.086	86.511	1.00	56.53	A	C
ATOM	2878	O	GLN A 372	67.558	143.063	85.469	1.00	57.38	A	O
ATOM	2879	N	PHE A 373	67.769	143.661	87.623	1.00	55.36	A	N
ATOM	2880	CA	PHE A 373	66.472	144.318	87.613	1.00	56.51	A	C
ATOM	2881	CB	PHE A 373	66.080	144.795	89.014	1.00	55.71	A	C
ATOM	2882	CG	PHE A 373	65.674	143.680	89.936	1.00	56.13	A	C
ATOM	2883	CD1	PHE A 373	66.438	143.369	91.056	1.00	55.83	A	C
ATOM	2884	CD2	PHE A 373	64.534	142.925	89.671	1.00	55.74	A	C
ATOM	2885	CE1	PHE A 373	66.075	142.322	91.897	1.00	55.19	A	C
ATOM	2886	CE2	PHE A 373	64.163	141.880	90.503	1.00	54.69	A	C
ATOM	2887	CZ	PHE A 373	64.935	141.576	91.619	1.00	55.79	A	C
ATOM	2888	C	PHE A 373	66.542	145.489	86.649	1.00	57.66	A	C
ATOM	2889	O	PHE A 373	65.570	145.786	85.959	1.00	57.75	A	O
ATOM	2890	N	LYS A 374	67.699	146.146	86.594	1.00	58.93	A	N
ATOM	2891	CA	LYS A 374	67.876	147.267	85.682	1.00	60.37	A	C
ATOM	2892	CB	LYS A 374	69.277	147.872	85.812	1.00	63.59	A	C
ATOM	2893	CG	LYS A 374	69.477	148.754	87.040	1.00	67.78	A	C
ATOM	2894	CD	LYS A 374	70.771	149.560	86.924	1.00	72.23	A	C
ATOM	2895	CE	LYS A 374	70.874	150.629	88.010	1.00	74.35	A	C
ATOM	2896	NZ	LYS A 374	71.949	151.631	87.710	1.00	76.30	A	N
ATOM	2897	C	LYS A 374	67.674	146.771	84.263	1.00	59.79	A	C
ATOM	2898	O	LYS A 374	66.987	147.407	83.465	1.00	60.52	A	O
ATOM	2899	N	THR A 375	68.268	145.625	83.954	1.00	58.08	A	N
ATOM	2900	CA	THR A 375	68.143	145.048	82.625	1.00	58.48	A	C
ATOM	2901	CB	THR A 375	69.025	143.789	82.476	1.00	57.57	A	C
ATOM	2902	OG1	THR A 375	70.390	144.121	82.757	1.00	58.66	A	O
ATOM	2903	CG2	THR A 375	68.930	143.237	81.065	1.00	55.34	A	C
ATOM	2904	C	THR A 375	66.693	144.667	82.353	1.00	58.68	A	C
ATOM	2905	O	THR A 375	66.180	144.878	81.256	1.00	59.45	A	O
ATOM	2906	N	ALA A 376	66.033	144.104	83.357	1.00	59.16	A	N
ATOM	2907	CA	ALA A 376	64.641	143.690	83.213	1.00	60.05	A	C
ATOM	2908	CB	ALA A 376	64.155	143.041	84.497	1.00	59.51	A	C
ATOM	2909	C	ALA A 376	63.748	144.874	82.861	1.00	61.02	A	C
ATOM	2910	O	ALA A 376	62.972	144.815	81.903	1.00	60.48	A	O
ATOM	2911	N	ASP A 377	63.855	145.942	83.649	1.00	61.57	A	N
ATOM	2912	CA	ASP A 377	63.061	147.139	83.421	1.00	63.48	A	C
ATOM	2913	CB	ASP A 377	63.314	148.171	84.524	1.00	66.43	A	C
ATOM	2914	CG	ASP A 377	62.529	147.875	85.796	1.00	69.11	A	C
ATOM	2915	OD1	ASP A 377	62.733	148.596	86.793	1.00	69.81	A	O
ATOM	2916	OD2	ASP A 377	61.706	146.931	85.800	1.00	71.04	A	O
ATOM	2917	C	ASP A 377	63.414	147.731	82.071	1.00	63.24	A	C
ATOM	2918	O	ASP A 377	62.529	148.085	81.290	1.00	63.25	A	O
ATOM	2919	N	LYS A 378	64.712	147.824	81.798	1.00	62.77	A	N
ATOM	2920	CA	LYS A 378	65.194	148.365	80.534	1.00	63.19	A	C
ATOM	2921	CB	LYS A 378	66.719	148.261	80.461	1.00	66.13	A	C
ATOM	2922	CG	LYS A 378	67.325	148.700	79.130	1.00	68.82	A	C
ATOM	2923	CD	LYS A 378	68.812	148.349	79.056	1.00	71.01	A	C
ATOM	2924	CE	LYS A 378	69.383	148.621	77.670	1.00	73.39	A	C
ATOM	2925	NZ	LYS A 378	69.290	150.063	77.280	1.00	75.28	A	N

FIGURE 11-58

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ATOM	2926	C	LYS	A	378	64.575	147.627	79.353	1.00	62.22	A	C
ATOM	2927	O	LYS	A	378	64.257	148.234	78.340	1.00	62.02	A	O
ATOM	2928	N	LEU	A	379	64.405	146.315	79.484	1.00	61.78	A	N
ATOM	2929	CA	LEU	A	379	63.821	145.526	78.410	1.00	60.34	A	C
ATOM	2930	CB	LEU	A	379	64.393	144.109	78.434	1.00	59.96	A	C
ATOM	2931	CG	LEU	A	379	65.899	143.943	78.203	1.00	61.44	A	C
ATOM	2932	CD1	LEU	A	379	66.277	142.472	78.345	1.00	58.02	A	C
ATOM	2933	CD2	LEU	A	379	66.277	144.468	76.822	1.00	59.99	A	C
ATOM	2934	C	LEU	A	379	62.292	145.490	78.494	1.00	60.37	A	C
ATOM	2935	O	LEU	A	379	61.631	144.768	77.745	1.00	59.55	A	O
ATOM	2936	N	GLN	A	380	61.736	146.277	79.410	1.00	60.24	A	N
ATOM	2937	CA	GLN	A	380	60.285	146.370	79.584	1.00	60.96	A	C
ATOM	2938	CB	GLN	A	380	59.638	147.006	78.347	1.00	63.37	A	C
ATOM	2939	CG	GLN	A	380	59.940	148.487	78.150	1.00	67.22	A	C
ATOM	2940	CD	GLN	A	380	59.210	149.079	76.946	1.00	70.69	A	C
ATOM	2941	OE1	GLN	A	380	59.303	150.284	76.678	1.00	71.11	A	O
ATOM	2942	NE2	GLN	A	380	58.480	148.234	76.213	1.00	69.40	A	N
ATOM	2943	C	GLN	A	380	59.581	145.053	79.869	1.00	59.26	A	C
ATOM	2944	O	GLN	A	380	58.415	144.883	79.505	1.00	58.39	A	O
ATOM	2945	N	ALA	A	381	60.277	144.125	80.516	1.00	58.00	A	N
ATOM	2946	CA	ALA	A	381	59.675	142.835	80.838	1.00	57.48	A	C
ATOM	2947	CB	ALA	A	381	60.619	142.016	81.706	1.00	56.15	A	C
ATOM	2948	C	ALA	A	381	58.353	143.059	81.565	1.00	57.44	A	C
ATOM	2949	O	ALA	A	381	58.259	143.909	82.453	1.00	56.03	A	O
ATOM	2950	N	LYS	A	382	57.330	142.309	81.174	1.00	58.12	A	N
ATOM	2951	CA	LYS	A	382	56.021	142.436	81.801	1.00	59.32	A	C
ATOM	2952	CB	LYS	A	382	54.946	141.779	80.935	1.00	61.24	A	C
ATOM	2953	CG	LYS	A	382	54.778	142.416	79.572	1.00	63.50	A	C
ATOM	2954	CD	LYS	A	382	53.734	141.686	78.753	1.00	65.85	A	C
ATOM	2955	CE	LYS	A	382	53.661	142.252	77.343	1.00	67.95	A	C
ATOM	2956	NZ	LYS	A	382	52.600	141.572	76.539	1.00	70.41	A	N
ATOM	2957	C	LYS	A	382	56.059	141.767	83.164	1.00	59.22	A	C
ATOM	2958	O	LYS	A	382	55.496	142.272	84.138	1.00	60.58	A	O
ATOM	2959	N	LEU	A	383	56.727	140.621	83.220	1.00	57.72	A	N
ATOM	2960	CA	LEU	A	383	56.862	139.872	84.460	1.00	55.78	A	C
ATOM	2961	CB	LEU	A	383	56.218	138.493	84.322	1.00	55.52	A	C
ATOM	2962	CG	LEU	A	383	54.705	138.429	84.147	1.00	54.82	A	C
ATOM	2963	CD1	LEU	A	383	54.314	137.043	83.680	1.00	54.81	A	C
ATOM	2964	CD2	LEU	A	383	54.030	138.781	85.461	1.00	55.62	A	C
ATOM	2965	C	LEU	A	383	58.340	139.703	84.780	1.00	55.01	A	C
ATOM	2966	O	LEU	A	383	59.178	139.618	83.885	1.00	53.89	A	O
ATOM	2967	N	VAL	A	384	58.651	139.657	86.065	1.00	55.23	A	N
ATOM	2968	CA	VAL	A	384	60.019	139.485	86.518	1.00	55.81	A	C
ATOM	2969	CB	VAL	A	384	60.596	140.788	87.123	1.00	56.47	A	C
ATOM	2970	CG1	VAL	A	384	61.982	140.532	87.696	1.00	56.09	A	C
ATOM	2971	CG2	VAL	A	384	60.678	141.859	86.059	1.00	56.82	A	C
ATOM	2972	C	VAL	A	384	59.991	138.417	87.589	1.00	55.67	A	C
ATOM	2973	O	VAL	A	384	59.368	138.591	88.635	1.00	56.12	A	O
ATOM	2974	N	LEU	A	385	60.651	137.303	87.307	1.00	56.07	A	N
ATOM	2975	CA	LEU	A	385	60.727	136.196	88.241	1.00	56.33	A	C
ATOM	2976	CB	LEU	A	385	60.577	134.866	87.493	1.00	54.39	A	C
ATOM	2977	CG	LEU	A	385	59.217	134.600	86.834	1.00	55.24	A	C
ATOM	2978	CD1	LEU	A	385	59.068	135.454	85.586	1.00	53.00	A	C
ATOM	2979	CD2	LEU	A	385	59.106	133.123	86.476	1.00	52.41	A	C
ATOM	2980	C	LEU	A	385	62.078	136.252	88.956	1.00	56.87	A	C
ATOM	2981	O	LEU	A	385	63.127	136.339	88.312	1.00	57.64	A	O
ATOM	2982	N	THR	A	386	62.057	136.214	90.283	1.00	56.55	A	N
ATOM	2983	CA	THR	A	386	63.303	136.257	91.042	1.00	57.18	A	C
ATOM	2984	CB	THR	A	386	63.336	137.422	92.039	1.00	57.51	A	C
ATOM	2985	OG1	THR	A	386	62.894	138.621	91.398	1.00	59.82	A	O
ATOM	2986	CG2	THR	A	386	64.749	137.617	92.567	1.00	56.97	A	C

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ATOM	2987	C	THR	A	386	63.482	134.993	91.856	1.00	57.32	A	C
ATOM	2988	O	THR	A	386	62.560	134.555	92.549	1.00	56.52	A	O
ATOM	2989	N	ILE	A	387	64.671	134.410	91.773	1.00	57.32	A	N
ATOM	2990	CA	ILE	A	387	64.962	133.212	92.532	1.00	58.57	A	C
ATOM	2991	CB	ILE	A	387	64.925	131.952	91.652	1.00	58.86	A	C
ATOM	2992	CG2	ILE	A	387	63.516	131.757	91.106	1.00	60.29	A	C
ATOM	2993	CG1	ILE	A	387	65.949	132.064	90.523	1.00	58.31	A	C
ATOM	2994	CD1	ILE	A	387	66.076	130.808	89.689	1.00	58.98	A	C
ATOM	2995	C	ILE	A	387	66.315	133.298	93.217	1.00	59.69	A	C
ATOM	2996	O	ILE	A	387	67.353	133.349	92.562	1.00	56.73	A	O
ATOM	2997	N	GLY	A	388	66.283	133.332	94.547	1.00	62.16	A	N
ATOM	2998	CA	GLY	A	388	67.503	133.389	95.329	1.00	65.89	A	C
ATOM	2999	C	GLY	A	388	67.792	132.014	95.904	1.00	68.91	A	C
ATOM	3000	O	GLY	A	388	67.018	131.076	95.692	1.00	67.08	A	O
ATOM	3001	N	GLU	A	389	68.907	131.883	96.622	1.00	72.33	A	N
ATOM	3002	CA	GLU	A	389	69.275	130.606	97.228	1.00	75.43	A	C
ATOM	3003	CB	GLU	A	389	70.553	130.755	98.064	1.00	77.78	A	C
ATOM	3004	CG	GLU	A	389	71.696	129.807	97.680	1.00	81.25	A	C
ATOM	3005	CD	GLU	A	389	72.742	130.462	96.781	1.00	83.64	A	C
ATOM	3006	OE1	GLU	A	389	73.146	131.611	97.078	1.00	83.36	A	O
ATOM	3007	OE2	GLU	A	389	73.172	129.825	95.790	1.00	84.64	A	O
ATOM	3008	C	GLU	A	389	68.126	130.150	98.127	1.00	75.44	A	C
ATOM	3009	O	GLU	A	389	67.792	128.965	98.183	1.00	75.30	A	O
ATOM	3010	N	ASN	A	390	67.523	131.110	98.823	1.00	75.38	A	N
ATOM	3011	CA	ASN	A	390	66.411	130.830	99.721	1.00	75.38	A	C
ATOM	3012	CB	ASN	A	390	66.115	132.062	100.596	1.00	78.10	A	C
ATOM	3013	CG	ASN	A	390	66.549	133.377	99.942	1.00	81.24	A	C
ATOM	3014	OD1	ASN	A	390	67.685	133.509	99.466	1.00	81.80	A	O
ATOM	3015	ND2	ASN	A	390	65.649	134.360	99.933	1.00	81.82	A	N
ATOM	3016	C	ASN	A	390	65.157	130.367	98.974	1.00	73.71	A	C
ATOM	3017	O	ASN	A	390	64.459	129.464	99.435	1.00	74.10	A	O
ATOM	3018	N	GLU	A	391	64.873	130.970	97.822	1.00	72.07	A	N
ATOM	3019	CA	GLU	A	391	63.710	130.568	97.033	1.00	69.69	A	C
ATOM	3020	CB	GLU	A	391	63.549	131.454	95.797	1.00	69.00	A	C
ATOM	3021	CG	GLU	A	391	63.036	132.870	96.059	1.00	68.48	A	C
ATOM	3022	CD	GLU	A	391	63.941	133.679	96.968	1.00	67.65	A	C
ATOM	3023	OE1	GLU	A	391	65.149	133.372	97.042	1.00	67.16	A	O
ATOM	3024	OE2	GLU	A	391	63.446	134.635	97.598	1.00	67.38	A	O
ATOM	3025	C	GLU	A	391	63.904	129.124	96.589	1.00	69.36	A	C
ATOM	3026	O	GLU	A	391	62.974	128.326	96.610	1.00	69.08	A	O
ATOM	3027	N	LEU	A	392	65.123	128.791	96.185	1.00	69.92	A	N
ATOM	3028	CA	LEU	A	392	65.418	127.436	95.748	1.00	71.08	A	C
ATOM	3029	CB	LEU	A	392	66.872	127.319	95.296	1.00	72.40	A	C
ATOM	3030	CG	LEU	A	392	67.205	127.954	93.948	1.00	72.55	A	C
ATOM	3031	CD1	LEU	A	392	68.622	127.575	93.573	1.00	73.84	A	C
ATOM	3032	CD2	LEU	A	392	66.227	127.469	92.886	1.00	72.51	A	C
ATOM	3033	C	LEU	A	392	65.146	126.421	96.847	1.00	71.49	A	C
ATOM	3034	O	LEU	A	392	64.473	125.417	96.610	1.00	71.23	A	O
ATOM	3035	N	ASN	A	393	65.681	126.676	98.042	1.00	71.79	A	N
ATOM	3036	CA	ASN	A	393	65.468	125.785	99.183	1.00	71.71	A	C
ATOM	3037	CB	ASN	A	393	65.686	126.521	100.513	1.00	72.37	A	C
ATOM	3038	CG	ASN	A	393	67.117	126.986	100.715	1.00	72.56	A	C
ATOM	3039	OD1	ASN	A	393	68.061	126.196	100.650	1.00	73.26	A	O
ATOM	3040	ND2	ASN	A	393	67.282	128.279	100.983	1.00	72.63	A	N
ATOM	3041	C	ASN	A	393	64.021	125.298	99.155	1.00	71.69	A	C
ATOM	3042	O	ASN	A	393	63.754	124.093	99.083	1.00	71.70	A	O
ATOM	3043	N	GLU	A	394	63.097	126.258	99.198	1.00	70.36	A	N
ATOM	3044	CA	GLU	A	394	61.673	125.961	99.200	1.00	69.08	A	C
ATOM	3045	CB	GLU	A	394	60.897	127.109	99.852	1.00	70.11	A	C
ATOM	3046	CG	GLU	A	394	59.429	126.768	100.090	1.00	73.61	A	C
ATOM	3047	CD	GLU	A	394	58.612	127.932	100.610	1.00	74.30	A	C

FIGURE 11-60

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ATOM	3048	OE1	GLU	A	394	57.375	127.766	100.726	1.00	74.30	A	O
ATOM	3049	OE2	GLU	A	394	59.200	129.000	100.904	1.00	74.64	A	O
ATOM	3050	C	GLU	A	394	61.088	125.678	97.816	1.00	67.39	A	C
ATOM	3051	O	GLU	A	394	59.869	125.540	97.672	1.00	66.42	A	O
ATOM	3052	N	GLY	A	395	61.947	125.584	96.803	1.00	65.74	A	N
ATOM	3053	CA	GLY	A	395	61.468	125.320	95.453	1.00	63.57	A	C
ATOM	3054	C	GLY	A	395	60.352	126.274	95.062	1.00	62.10	A	C
ATOM	3055	O	GLY	A	395	59.292	125.859	94.581	1.00	61.45	A	O
ATOM	3056	N	ILE	A	396	60.606	127.562	95.266	1.00	60.92	A	N
ATOM	3057	CA	ILE	A	396	59.642	128.611	94.969	1.00	60.40	A	C
ATOM	3058	CB	ILE	A	396	59.050	129.157	96.301	1.00	61.57	A	C
ATOM	3059	CG2	ILE	A	396	58.705	130.639	96.195	1.00	61.75	A	C
ATOM	3060	CG1	ILE	A	396	57.839	128.301	96.691	1.00	62.07	A	C
ATOM	3061	CD1	ILE	A	396	57.099	128.780	97.920	1.00	63.72	A	C
ATOM	3062	C	ILE	A	396	60.267	129.738	94.149	1.00	58.89	A	C
ATOM	3063	O	ILE	A	396	61.485	129.885	94.117	1.00	58.38	A	O
ATOM	3064	N	VAL	A	397	59.426	130.524	93.481	1.00	58.58	A	N
ATOM	3065	CA	VAL	A	397	59.887	131.645	92.660	1.00	57.41	A	C
ATOM	3066	CB	VAL	A	397	59.943	131.246	91.153	1.00	56.14	A	C
ATOM	3067	CG1	VAL	A	397	58.591	130.725	90.708	1.00	52.57	A	C
ATOM	3068	CG2	VAL	A	397	60.352	132.448	90.301	1.00	54.94	A	C
ATOM	3069	C	VAL	A	397	58.961	132.854	92.815	1.00	56.98	A	C
ATOM	3070	O	VAL	A	397	57.743	132.708	92.765	1.00	55.73	A	O
ATOM	3071	N	ASN	A	398	59.537	134.042	93.001	1.00	57.25	A	N
ATOM	3072	CA	ASN	A	398	58.731	135.256	93.147	1.00	58.53	A	C
ATOM	3073	CB	ASN	A	398	59.453	136.283	94.025	1.00	60.16	A	C
ATOM	3074	CG	ASN	A	398	59.646	135.800	95.461	1.00	63.30	A	C
ATOM	3075	OD1	ASN	A	398	58.731	135.224	96.064	1.00	64.34	A	O
ATOM	3076	ND2	ASN	A	398	60.832	136.050	96.022	1.00	60.54	A	N
ATOM	3077	C	ASN	A	398	58.410	135.882	91.787	1.00	59.54	A	C
ATOM	3078	O	ASN	A	398	59.312	136.275	91.041	1.00	60.00	A	O
ATOM	3079	N	VAL	A	399	57.123	135.974	91.464	1.00	59.53	A	N
ATOM	3080	CA	VAL	A	399	56.702	136.545	90.189	1.00	59.41	A	C
ATOM	3081	CB	VAL	A	399	55.686	135.632	89.465	1.00	57.18	A	C
ATOM	3082	CG1	VAL	A	399	55.427	136.154	88.064	1.00	55.71	A	C
ATOM	3083	CG2	VAL	A	399	56.206	134.211	89.409	1.00	56.52	A	C
ATOM	3084	C	VAL	A	399	56.068	137.915	90.394	1.00	60.49	A	C
ATOM	3085	O	VAL	A	399	54.976	138.024	90.937	1.00	60.85	A	O
ATOM	3086	N	LYS	A	400	56.761	138.956	89.942	1.00	62.64	A	N
ATOM	3087	CA	LYS	A	400	56.285	140.327	90.084	1.00	64.52	A	C
ATOM	3088	CB	LYS	A	400	57.414	141.205	90.633	1.00	63.85	A	C
ATOM	3089	CG	LYS	A	400	57.031	142.652	90.914	1.00	64.30	A	C
ATOM	3090	CD	LYS	A	400	58.238	143.435	91.423	1.00	63.79	A	C
ATOM	3091	CE	LYS	A	400	57.955	144.923	91.512	1.00	63.61	A	C
ATOM	3092	NZ	LYS	A	400	59.179	145.682	91.908	1.00	65.99	A	N
ATOM	3093	C	LYS	A	400	55.778	140.896	88.759	1.00	66.20	A	C
ATOM	3094	O	LYS	A	400	56.404	140.711	87.708	1.00	64.79	A	O
ATOM	3095	N	SER	A	401	54.634	141.576	88.819	1.00	67.79	A	N
ATOM	3096	CA	SER	A	401	54.029	142.190	87.639	1.00	70.72	A	C
ATOM	3097	CB	SER	A	401	52.502	142.135	87.732	1.00	71.89	A	C
ATOM	3098	OG	SER	A	401	51.901	142.842	86.657	1.00	72.69	A	O
ATOM	3099	C	SER	A	401	54.478	143.641	87.551	1.00	71.41	A	C
ATOM	3100	O	SER	A	401	54.005	144.483	88.309	1.00	71.62	A	O
ATOM	3101	N	MET	A	402	55.387	143.931	86.625	1.00	72.51	A	N
ATOM	3102	CA	MET	A	402	55.903	145.285	86.469	1.00	74.30	A	C
ATOM	3103	CB	MET	A	402	56.924	145.339	85.328	1.00	74.65	A	C
ATOM	3104	CG	MET	A	402	58.096	144.390	85.532	1.00	75.26	A	C
ATOM	3105	SD	MET	A	402	58.576	144.268	87.274	1.00	75.52	A	S
ATOM	3106	CE	MET	A	402	59.337	145.881	87.540	1.00	76.51	A	C
ATOM	3107	C	MET	A	402	54.802	146.306	86.233	1.00	74.77	A	C
ATOM	3108	O	MET	A	402	55.020	147.507	86.384	1.00	74.57	A	O

FIGURE 11-61

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ATOM	3109	N	ALA A 403	53.620	145.826	85.861	1.00	75.46	A	N
ATOM	3110	CA	ALA A 403	52.488	146.710	85.633	1.00	76.29	A	C
ATOM	3111	CB	ALA A 403	51.387	145.969	84.879	1.00	76.40	A	C
ATOM	3112	C	ALA A 403	51.966	147.218	86.980	1.00	76.87	A	C
ATOM	3113	O	ALA A 403	51.986	148.415	87.246	1.00	77.27	A	O
ATOM	3114	N	THR A 404	51.517	146.303	87.835	1.00	78.12	A	N
ATOM	3115	CA	THR A 404	50.987	146.674	89.148	1.00	79.78	A	C
ATOM	3116	CB	THR A 404	49.973	145.632	89.658	1.00	79.75	A	C
ATOM	3117	OG1	THR A 404	50.671	144.442	90.052	1.00	81.04	A	O
ATOM	3118	CG2	THR A 404	48.965	145.289	88.564	1.00	79.17	A	C
ATOM	3119	C	THR A 404	52.079	146.809	90.208	1.00	80.96	A	C
ATOM	3120	O	THR A 404	51.862	147.410	91.261	1.00	81.19	A	O
ATOM	3121	N	ARG A 405	53.246	146.238	89.925	1.00	82.13	A	N
ATOM	3122	CA	ARG A 405	54.387	146.269	90.838	1.00	83.06	A	C
ATOM	3123	CB	ARG A 405	54.621	147.685	91.371	1.00	84.67	A	C
ATOM	3124	CG	ARG A 405	54.747	148.733	90.283	1.00	88.01	A	C
ATOM	3125	CD	ARG A 405	54.845	150.128	90.875	1.00	91.23	A	C
ATOM	3126	NE	ARG A 405	54.525	151.159	89.891	1.00	93.00	A	N
ATOM	3127	CZ	ARG A 405	54.479	152.462	90.157	1.00	94.27	A	C
ATOM	3128	NH1	ARG A 405	54.738	152.904	91.383	1.00	94.56	A	N
ATOM	3129	NH2	ARG A 405	54.162	153.324	89.198	1.00	94.96	A	N
ATOM	3130	C	ARG A 405	54.150	145.312	91.996	1.00	82.54	A	C
ATOM	3131	O	ARG A 405	54.753	145.440	93.064	1.00	82.65	A	O
ATOM	3132	N	GLU A 406	53.266	144.347	91.772	1.00	82.23	A	N
ATOM	3133	CA	GLU A 406	52.947	143.356	92.788	1.00	81.76	A	C
ATOM	3134	CB	GLU A 406	51.436	143.283	92.994	1.00	82.58	A	C
ATOM	3135	CG	GLU A 406	51.000	142.133	93.882	1.00	84.03	A	C
ATOM	3136	CD	GLU A 406	49.558	142.254	94.326	1.00	85.02	A	C
ATOM	3137	OE1	GLU A 406	49.024	141.279	94.897	1.00	85.57	A	O
ATOM	3138	OE2	GLU A 406	48.961	143.329	94.111	1.00	85.41	A	O
ATOM	3139	C	GLU A 406	53.476	141.979	92.409	1.00	80.88	A	C
ATOM	3140	O	GLU A 406	53.392	141.567	91.253	1.00	80.82	A	O
ATOM	3141	N	GLU A 407	54.028	141.272	93.389	1.00	79.97	A	N
ATOM	3142	CA	GLU A 407	54.555	139.938	93.152	1.00	78.81	A	C
ATOM	3143	CB	GLU A 407	56.081	139.932	93.262	1.00	78.70	A	C
ATOM	3144	CG	GLU A 407	56.639	140.519	94.538	1.00	79.23	A	C
ATOM	3145	CD	GLU A 407	58.159	140.541	94.533	1.00	79.64	A	C
ATOM	3146	OE1	GLU A 407	58.774	139.452	94.480	1.00	78.21	A	O
ATOM	3147	OE2	GLU A 407	58.737	141.650	94.575	1.00	79.62	A	O
ATOM	3148	C	GLU A 407	53.967	138.915	94.109	1.00	77.72	A	C
ATOM	3149	O	GLU A 407	53.650	139.226	95.259	1.00	77.74	A	O
ATOM	3150	N	LYS A 408	53.817	137.693	93.612	1.00	76.42	A	N
ATOM	3151	CA	LYS A 408	53.269	136.593	94.393	1.00	75.36	A	C
ATOM	3152	CB	LYS A 408	51.906	136.184	93.824	1.00	76.46	A	C
ATOM	3153	CG	LYS A 408	51.269	134.966	94.475	1.00	77.08	A	C
ATOM	3154	CD	LYS A 408	49.894	134.685	93.872	1.00	77.88	A	C
ATOM	3155	CE	LYS A 408	49.414	133.277	94.205	1.00	78.12	A	C
ATOM	3156	NZ	LYS A 408	49.448	133.002	95.671	1.00	78.57	A	N
ATOM	3157	C	LYS A 408	54.243	135.425	94.328	1.00	73.99	A	C
ATOM	3158	O	LYS A 408	54.808	135.143	93.271	1.00	74.17	A	O
ATOM	3159	N	ALA A 409	54.453	134.759	95.458	1.00	71.80	A	N
ATOM	3160	CA	ALA A 409	55.369	133.626	95.500	1.00	70.07	A	C
ATOM	3161	CB	ALA A 409	55.767	133.316	96.944	1.00	69.16	A	C
ATOM	3162	C	ALA A 409	54.707	132.411	94.859	1.00	68.49	A	C
ATOM	3163	O	ALA A 409	53.517	132.159	95.061	1.00	67.71	A	O
ATOM	3164	N	PHE A 410	55.485	131.669	94.077	1.00	66.72	A	N
ATOM	3165	CA	PHE A 410	54.979	130.482	93.402	1.00	65.19	A	C
ATOM	3166	CB	PHE A 410	54.741	130.741	91.915	1.00	64.52	A	C
ATOM	3167	CG	PHE A 410	53.511	131.535	91.614	1.00	64.74	A	C
ATOM	3168	CD1	PHE A 410	53.501	132.913	91.772	1.00	64.18	A	C
ATOM	3169	CD2	PHE A 410	52.376	130.904	91.119	1.00	65.14	A	C

FIGURE 11-62

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ATOM	3170	CE1	PHE	A	410	52.381	133.658	91.435	1.00	64.97	A	C
ATOM	3171	CE2	PHE	A	410	51.250	131.636	90.778	1.00	66.74	A	C
ATOM	3172	CZ	PHE	A	410	51.253	133.021	90.936	1.00	67.31	A	C
ATOM	3173	C	PHE	A	410	55.934	129.311	93.487	1.00	64.56	A	C
ATOM	3174	O	PHE	A	410	57.133	129.471	93.725	1.00	64.13	A	O
ATOM	3175	N	PRO	A	411	55.401	128.100	93.304	1.00	63.88	A	N
ATOM	3176	CD	PRO	A	411	53.971	127.738	93.328	1.00	63.51	A	C
ATOM	3177	CA	PRO	A	411	56.246	126.911	93.349	1.00	62.60	A	C
ATOM	3178	CB	PRO	A	411	55.256	125.808	93.699	1.00	62.99	A	C
ATOM	3179	CG	PRO	A	411	54.008	126.262	93.003	1.00	63.95	A	C
ATOM	3180	C	PRO	A	411	56.831	126.755	91.946	1.00	60.94	A	C
ATOM	3181	O	PRO	A	411	56.125	126.934	90.954	1.00	59.44	A	O
ATOM	3182	N	LEU	A	412	58.119	126.450	91.860	1.00	60.39	A	N
ATOM	3183	CA	LEU	A	412	58.752	126.282	90.560	1.00	59.03	A	C
ATOM	3184	CB	LEU	A	412	60.107	125.603	90.732	1.00	57.99	A	C
ATOM	3185	CG	LEU	A	412	61.099	126.434	91.550	1.00	58.46	A	C
ATOM	3186	CD1	LEU	A	412	62.410	125.670	91.696	1.00	56.90	A	C
ATOM	3187	CD2	LEU	A	412	61.329	127.777	90.864	1.00	57.42	A	C
ATOM	3188	C	LEU	A	412	57.874	125.472	89.607	1.00	59.13	A	C
ATOM	3189	O	LEU	A	412	57.664	125.866	88.456	1.00	58.76	A	O
ATOM	3190	N	SER	A	413	57.346	124.354	90.100	1.00	58.38	A	N
ATOM	3191	CA	SER	A	413	56.498	123.477	89.298	1.00	57.80	A	C
ATOM	3192	CB	SER	A	413	55.868	122.396	90.184	1.00	58.07	A	C
ATOM	3193	OG	SER	A	413	54.976	122.970	91.125	1.00	60.02	A	O
ATOM	3194	C	SER	A	413	55.395	124.244	88.574	1.00	56.55	A	C
ATOM	3195	O	SER	A	413	54.987	123.877	87.472	1.00	55.71	A	O
ATOM	3196	N	ALA	A	414	54.908	125.307	89.201	1.00	55.51	A	N
ATOM	3197	CA	ALA	A	414	53.855	126.115	88.603	1.00	56.43	A	C
ATOM	3198	CB	ALA	A	414	53.449	127.234	89.561	1.00	55.40	A	C
ATOM	3199	C	ALA	A	414	54.338	126.700	87.271	1.00	57.38	A	C
ATOM	3200	O	ALA	A	414	53.599	126.706	86.278	1.00	55.58	A	O
ATOM	3201	N	ILE	A	415	55.583	127.180	87.260	1.00	57.61	A	N
ATOM	3202	CA	ILE	A	415	56.174	127.772	86.064	1.00	58.71	A	C
ATOM	3203	CB	ILE	A	415	57.521	128.479	86.380	1.00	59.61	A	C
ATOM	3204	CG2	ILE	A	415	58.101	129.088	85.105	1.00	56.11	A	C
ATOM	3205	CG1	ILE	A	415	57.322	129.549	87.459	1.00	57.45	A	C
ATOM	3206	CD1	ILE	A	415	56.355	130.637	87.079	1.00	58.37	A	C
ATOM	3207	C	ILE	A	415	56.438	126.730	84.985	1.00	59.74	A	C
ATOM	3208	O	ILE	A	415	56.122	126.942	83.814	1.00	59.56	A	O
ATOM	3209	N	HIS	A	416	57.022	125.605	85.376	1.00	60.67	A	N
ATOM	3210	CA	HIS	A	416	57.330	124.564	84.410	1.00	62.87	A	C
ATOM	3211	CB	HIS	A	416	58.292	123.550	85.027	1.00	63.43	A	C
ATOM	3212	CG	HIS	A	416	59.544	124.161	85.579	1.00	66.10	A	C
ATOM	3213	CD2	HIS	A	416	60.831	124.091	85.161	1.00	66.41	A	C
ATOM	3214	ND1	HIS	A	416	59.550	124.959	86.702	1.00	66.86	A	N
ATOM	3215	CE1	HIS	A	416	60.786	125.352	86.953	1.00	66.36	A	C
ATOM	3216	NE2	HIS	A	416	61.582	124.839	86.033	1.00	65.39	A	N
ATOM	3217	C	HIS	A	416	56.088	123.845	83.885	1.00	63.87	A	C
ATOM	3218	O	HIS	A	416	55.945	123.638	82.680	1.00	63.14	A	O
ATOM	3219	N	ASP	A	417	55.183	123.481	84.788	1.00	65.44	A	N
ATOM	3220	CA	ASP	A	417	53.981	122.756	84.394	1.00	67.04	A	C
ATOM	3221	CB	ASP	A	417	53.507	121.840	85.530	1.00	67.61	A	C
ATOM	3222	CG	ASP	A	417	54.552	120.814	85.929	1.00	68.75	A	C
ATOM	3223	OD1	ASP	A	417	55.316	120.365	85.042	1.00	69.75	A	O
ATOM	3224	OD2	ASP	A	417	54.602	120.447	87.126	1.00	68.98	A	O
ATOM	3225	C	ASP	A	417	52.822	123.626	83.937	1.00	67.35	A	C
ATOM	3226	O	ASP	A	417	51.855	123.119	83.366	1.00	67.14	A	O
ATOM	3227	N	SER	A	418	52.901	124.930	84.174	1.00	68.19	A	N
ATOM	3228	CA	SER	A	418	51.809	125.797	83.751	1.00	68.64	A	C
ATOM	3229	CB	SER	A	418	50.529	125.408	84.504	1.00	69.77	A	C
ATOM	3230	OG	SER	A	418	50.775	125.255	85.894	1.00	70.29	A	O

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ATOM	3231	C	SER	A	418	52.058	127.294	83.887	1.00	68.16	A	C
ATOM	3232	O	SER	A	418	51.391	127.975	84.666	1.00	68.26	A	O
ATOM	3233	N	PHE	A	419	53.017	127.806	83.124	1.00	68.06	A	N
ATOM	3234	CA	PHE	A	419	53.312	129.233	83.151	1.00	68.32	A	C
ATOM	3235	CB	PHE	A	419	54.548	129.537	82.304	1.00	65.44	A	C
ATOM	3236	CG	PHE	A	419	54.968	130.975	82.348	1.00	63.12	A	C
ATOM	3237	CD1	PHE	A	419	55.331	131.569	83.555	1.00	62.31	A	C
ATOM	3238	CD2	PHE	A	419	54.989	131.741	81.192	1.00	58.49	A	C
ATOM	3239	CE1	PHE	A	419	55.708	132.905	83.604	1.00	61.66	A	C
ATOM	3240	CE2	PHE	A	419	55.362	133.070	81.232	1.00	59.17	A	C
ATOM	3241	CZ	PHE	A	419	55.723	133.658	82.439	1.00	59.43	A	C
ATOM	3242	C	PHE	A	419	52.082	129.921	82.562	1.00	70.06	A	C
ATOM	3243	O	PHE	A	419	51.742	131.057	82.908	1.00	69.08	A	O
ATOM	3244	N	ASP	A	420	51.426	129.192	81.665	1.00	73.01	A	N
ATOM	3245	CA	ASP	A	420	50.206	129.622	80.996	1.00	75.09	A	C
ATOM	3246	CB	ASP	A	420	49.525	128.389	80.391	1.00	76.65	A	C
ATOM	3247	CG	ASP	A	420	48.356	128.736	79.492	1.00	79.28	A	C
ATOM	3248	OD1	ASP	A	420	47.437	129.452	79.944	1.00	80.68	A	O
ATOM	3249	OD2	ASP	A	420	48.352	128.278	78.328	1.00	80.61	A	O
ATOM	3250	C	ASP	A	420	49.290	130.258	82.041	1.00	76.01	A	C
ATOM	3251	O	ASP	A	420	48.761	131.355	81.843	1.00	75.80	A	O
ATOM	3252	N	GLU	A	421	49.135	129.556	83.162	1.00	76.56	A	N
ATOM	3253	CA	GLU	A	421	48.280	129.981	84.271	1.00	77.80	A	C
ATOM	3254	CB	GLU	A	421	48.055	128.803	85.230	1.00	78.98	A	C
ATOM	3255	CG	GLU	A	421	47.894	127.441	84.549	1.00	80.33	A	C
ATOM	3256	CD	GLU	A	421	46.450	127.061	84.297	1.00	80.22	A	C
ATOM	3257	OE1	GLU	A	421	45.694	126.927	85.284	1.00	80.96	A	O
ATOM	3258	OE2	GLU	A	421	46.076	126.890	83.115	1.00	80.37	A	O
ATOM	3259	C	GLU	A	421	48.849	131.157	85.067	1.00	77.92	A	C
ATOM	3260	O	GLU	A	421	48.144	132.132	85.334	1.00	77.85	A	O
ATOM	3261	N	VAL	A	422	50.118	131.052	85.460	1.00	77.84	A	N
ATOM	3262	CA	VAL	A	422	50.771	132.102	86.242	1.00	77.40	A	C
ATOM	3263	CB	VAL	A	422	52.253	131.749	86.545	1.00	77.03	A	C
ATOM	3264	CG1	VAL	A	422	52.883	132.833	87.402	1.00	75.87	A	C
ATOM	3265	CG2	VAL	A	422	52.336	130.407	87.259	1.00	76.01	A	C
ATOM	3266	C	VAL	A	422	50.723	133.446	85.522	1.00	77.78	A	C
ATOM	3267	O	VAL	A	422	50.536	134.490	86.148	1.00	76.95	A	O
ATOM	3268	N	TYR	A	423	50.891	133.419	84.206	1.00	78.27	A	N
ATOM	3269	CA	TYR	A	423	50.854	134.649	83.430	1.00	79.64	A	C
ATOM	3270	CB	TYR	A	423	51.034	134.342	81.941	1.00	80.33	A	C
ATOM	3271	CG	TYR	A	423	51.166	135.569	81.063	1.00	80.88	A	C
ATOM	3272	CD1	TYR	A	423	52.355	136.294	81.017	1.00	81.22	A	C
ATOM	3273	CE1	TYR	A	423	52.486	137.416	80.196	1.00	81.69	A	C
ATOM	3274	CD2	TYR	A	423	50.103	135.999	80.269	1.00	81.34	A	C
ATOM	3275	CE2	TYR	A	423	50.223	137.119	79.446	1.00	81.83	A	C
ATOM	3276	CZ	TYR	A	423	51.417	137.820	79.414	1.00	82.04	A	C
ATOM	3277	OH	TYR	A	423	51.540	138.920	78.595	1.00	82.85	A	O
ATOM	3278	C	TYR	A	423	49.513	135.344	83.655	1.00	79.96	A	C
ATOM	3279	O	TYR	A	423	49.454	136.420	84.256	1.00	79.85	A	O
ATOM	3280	N	ASP	A	424	48.440	134.713	83.185	1.00	80.28	A	N
ATOM	3281	CA	ASP	A	424	47.095	135.264	83.317	1.00	80.96	A	C
ATOM	3282	CB	ASP	A	424	46.060	134.216	82.916	1.00	82.15	A	C
ATOM	3283	CG	ASP	A	424	46.207	133.783	81.476	1.00	83.83	A	C
ATOM	3284	OD1	ASP	A	424	46.285	134.668	80.596	1.00	83.75	A	O
ATOM	3285	OD2	ASP	A	424	46.242	132.561	81.223	1.00	85.42	A	O
ATOM	3286	C	ASP	A	424	46.779	135.788	84.712	1.00	80.51	A	C
ATOM	3287	O	ASP	A	424	46.324	136.921	84.866	1.00	80.08	A	O
ATOM	3288	N	GLU	A	425	47.015	134.961	85.724	1.00	80.77	A	N
ATOM	3289	CA	GLU	A	425	46.755	135.357	87.103	1.00	81.36	A	C
ATOM	3290	CB	GLU	A	425	47.158	134.228	88.058	1.00	80.76	A	C
ATOM	3291	CG	GLU	A	425	47.212	134.627	89.533	1.00	81.08	A	C

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ATOM	3292	CD	GLU	A	425	47.502	133.448	90.457	1.00	81.15	A	C
ATOM	3293	OE1	GLU	A	425	47.907	133.690	91.618	1.00	79.35	A	O
ATOM	3294	OE2	GLU	A	425	47.316	132.284	90.027	1.00	81.14	A	O
ATOM	3295	C	GLU	A	425	47.500	136.639	87.459	1.00	82.82	A	C
ATOM	3296	O	GLU	A	425	46.920	137.556	88.040	1.00	82.59	A	O
ATOM	3297	N	MET	A	426	48.780	136.707	87.096	1.00	84.89	A	N
ATOM	3298	CA	MET	A	426	49.602	137.879	87.393	1.00	86.13	A	C
ATOM	3299	CB	MET	A	426	51.085	137.518	87.325	1.00	84.82	A	C
ATOM	3300	CG	MET	A	426	51.536	136.584	88.434	1.00	83.33	A	C
ATOM	3301	SD	MET	A	426	51.031	137.151	90.077	1.00	82.46	A	S
ATOM	3302	CE	MET	A	426	52.174	138.494	90.369	1.00	81.48	A	C
ATOM	3303	C	MET	A	426	49.333	139.094	86.510	1.00	88.28	A	C
ATOM	3304	O	MET	A	426	49.510	140.232	86.953	1.00	89.17	A	O
ATOM	3305	N	MET	A	427	48.921	138.866	85.265	1.00	89.80	A	N
ATOM	3306	CA	MET	A	427	48.619	139.978	84.366	1.00	91.81	A	C
ATOM	3307	CB	MET	A	427	48.497	139.489	82.920	1.00	91.94	A	C
ATOM	3308	CG	MET	A	427	49.831	139.147	82.268	1.00	92.17	A	C
ATOM	3309	SD	MET	A	427	50.929	140.580	82.116	1.00	91.75	A	S
ATOM	3310	CE	MET	A	427	51.774	140.530	83.679	1.00	91.49	A	C
ATOM	3311	C	MET	A	427	47.317	140.639	84.810	1.00	92.89	A	C
ATOM	3312	O	MET	A	427	47.279	141.314	85.841	1.00	93.85	A	O
ATOM	3313	N	THR	A	428	46.254	140.448	84.036	1.00	93.67	A	N
ATOM	3314	CA	THR	A	428	44.958	141.019	84.383	1.00	94.14	A	C
ATOM	3315	CB	THR	A	428	43.941	140.863	83.221	1.00	94.34	A	C
ATOM	3316	OG1	THR	A	428	44.196	139.641	82.516	1.00	94.34	A	O
ATOM	3317	CG2	THR	A	428	44.037	142.047	82.260	1.00	93.90	A	C
ATOM	3318	C	THR	A	428	44.409	140.352	85.650	1.00	94.43	A	C
ATOM	3319	O	THR	A	428	43.626	139.383	85.533	1.00	94.69	A	O
ATOM	3320	OXT	THR	A	428	44.793	140.795	86.755	1.00	94.15	A	O
TER	3321		THR	A	428						A	
ATOM	3322	CB	ALA	A	999	69.262	156.347	40.713	1.00	69.50	A	C
ATOM	3323	C	ALA	A	999	67.800	156.250	38.664	1.00	71.70	A	C
ATOM	3324	O	ALA	A	999	67.696	157.000	37.686	1.00	73.37	A	O
ATOM	3325	N	ALA	A	999	66.802	156.458	40.943	1.00	70.69	A	N
ATOM	3326	CA	ALA	A	999	67.956	156.831	40.077	1.00	71.32	A	C
ATOM	3327	N	HIS	A	1000	67.786	154.922	38.556	1.00	70.84	A	N
ATOM	3328	CA	HIS	A	1000	67.643	154.250	37.261	1.00	69.70	A	C
ATOM	3329	CB	HIS	A	1000	68.940	154.374	36.440	1.00	73.75	A	C
ATOM	3330	CG	HIS	A	1000	70.162	154.637	37.268	1.00	77.03	A	C
ATOM	3331	CD2	HIS	A	1000	71.005	155.698	37.297	1.00	77.74	A	C
ATOM	3332	ND1	HIS	A	1000	70.613	153.762	38.234	1.00	78.83	A	N
ATOM	3333	CE1	HIS	A	1000	71.680	154.274	38.824	1.00	79.59	A	C
ATOM	3334	NE2	HIS	A	1000	71.938	155.448	38.275	1.00	79.27	A	N
ATOM	3335	C	HIS	A	1000	67.274	152.779	37.416	1.00	66.69	A	C
ATOM	3336	O	HIS	A	1000	68.038	151.996	37.978	1.00	67.01	A	O
ATOM	3337	N	HIS	A	1001	66.105	152.417	36.894	1.00	63.01	A	N
ATOM	3338	CA	HIS	A	1001	65.574	151.056	36.959	1.00	59.50	A	C
ATOM	3339	CB	HIS	A	1001	64.213	151.017	36.264	1.00	55.64	A	C
ATOM	3340	CG	HIS	A	1001	63.551	149.672	36.266	1.00	49.55	A	C
ATOM	3341	CD2	HIS	A	1001	63.833	148.534	36.944	1.00	49.16	A	C
ATOM	3342	ND1	HIS	A	1001	62.483	149.374	35.445	1.00	46.95	A	N
ATOM	3343	CE1	HIS	A	1001	62.141	148.109	35.609	1.00	45.23	A	C
ATOM	3344	NE2	HIS	A	1001	62.945	147.576	36.513	1.00	47.59	A	N
ATOM	3345	C	HIS	A	1001	66.484	149.981	36.364	1.00	59.45	A	C
ATOM	3346	O	HIS	A	1001	67.052	149.161	37.081	1.00	60.04	A	O
ATOM	3347	N	HIS	A	1002	66.616	149.969	35.052	1.00	59.28	A	N
ATOM	3348	CA	HIS	A	1002	67.450	148.963	34.412	1.00	60.05	A	C
ATOM	3349	CB	HIS	A	1002	66.680	148.406	33.205	1.00	60.19	A	C
ATOM	3350	CG	HIS	A	1002	67.451	147.443	32.354	1.00	58.74	A	C
ATOM	3351	CD2	HIS	A	1002	67.664	147.417	31.017	1.00	56.41	A	C
ATOM	3352	ND1	HIS	A	1002	68.057	146.312	32.861	1.00	57.18	A	N

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ATOM	3353	CE1	HIS	A1002	68.607	145.632	31.872	1.00	55.88	A	C
ATOM	3354	NE2	HIS	A1002	68.383	146.281	30.743	1.00	55.24	A	N
ATOM	3355	C	HIS	A1002	68.809	149.553	34.012	1.00	61.11	A	C
ATOM	3356	O	HIS	A1002	69.044	150.757	34.151	1.00	59.85	A	O
ATOM	3357	N	ALA	A1003	69.700	148.685	33.541	1.00	63.46	A	N
ATOM	3358	CA	ALA	A1003	71.044	149.058	33.096	1.00	65.24	A	C
ATOM	3359	CB	ALA	A1003	70.990	149.560	31.638	1.00	65.10	A	C
ATOM	3360	C	ALA	A1003	71.727	150.096	33.993	1.00	65.89	A	C
ATOM	3361	O	ALA	A1003	72.139	151.151	33.456	1.00	65.88	A	O
ATOM	3362	OXT	ALA	A1003	71.857	149.832	35.214	1.00	64.31	A	O
TER	3363		ALA	A1003						A	
ATOM	3364	CB	LYS	B 5	73.188	130.978	33.215	1.00	83.75	B	C
ATOM	3365	CG	LYS	B 5	72.456	130.607	31.929	1.00	83.31	B	C
ATOM	3366	CD	LYS	B 5	72.457	131.746	30.928	1.00	82.36	B	C
ATOM	3367	CE	LYS	B 5	71.502	131.460	29.784	1.00	81.42	B	C
ATOM	3368	NZ	LYS	B 5	71.400	132.618	28.855	1.00	81.99	B	N
ATOM	3369	C	LYS	B 5	74.409	129.557	34.863	1.00	85.59	B	C
ATOM	3370	O	LYS	B 5	74.958	128.513	34.493	1.00	86.09	B	O
ATOM	3371	N	LYS	B 5	72.121	130.444	35.399	1.00	84.31	B	N
ATOM	3372	CA	LYS	B 5	73.032	129.937	34.332	1.00	84.86	B	C
ATOM	3373	N	PRO	B 6	74.989	130.396	35.739	1.00	85.91	B	N
ATOM	3374	CD	PRO	B 6	74.506	131.707	36.210	1.00	86.09	B	C
ATOM	3375	CA	PRO	B 6	76.314	130.102	36.296	1.00	85.70	B	C
ATOM	3376	CB	PRO	B 6	76.516	131.224	37.312	1.00	85.64	B	C
ATOM	3377	CG	PRO	B 6	75.783	132.367	36.679	1.00	85.79	B	C
ATOM	3378	C	PRO	B 6	76.426	128.716	36.929	1.00	85.00	B	C
ATOM	3379	O	PRO	B 6	75.586	128.308	37.733	1.00	84.23	B	O
ATOM	3380	N	LYS	B 7	77.470	127.991	36.548	1.00	84.65	B	N
ATOM	3381	CA	LYS	B 7	77.702	126.660	37.084	1.00	83.87	B	C
ATOM	3382	CB	LYS	B 7	78.947	126.060	36.436	1.00	84.81	B	C
ATOM	3383	CG	LYS	B 7	78.752	125.556	35.008	1.00	84.86	B	C
ATOM	3384	CD	LYS	B 7	78.157	124.156	35.004	1.00	84.59	B	C
ATOM	3385	CE	LYS	B 7	78.290	123.500	33.640	1.00	84.23	B	C
ATOM	3386	NZ	LYS	B 7	77.908	122.063	33.698	1.00	83.92	B	N
ATOM	3387	C	LYS	B 7	77.895	126.759	38.594	1.00	82.95	B	C
ATOM	3388	O	LYS	B 7	78.518	127.700	39.085	1.00	83.04	B	O
ATOM	3389	N	GLY	B 8	77.351	125.793	39.326	1.00	82.03	B	N
ATOM	3390	CA	GLY	B 8	77.488	125.801	40.772	1.00	81.26	B	C
ATOM	3391	C	GLY	B 8	76.521	126.745	41.464	1.00	80.93	B	C
ATOM	3392	O	GLY	B 8	76.655	127.024	42.662	1.00	81.36	B	O
ATOM	3393	N	THR	B 9	75.549	127.251	40.711	1.00	78.83	B	N
ATOM	3394	CA	THR	B 9	74.552	128.153	41.271	1.00	77.09	B	C
ATOM	3395	CB	THR	B 9	74.794	129.630	40.849	1.00	79.21	B	C
ATOM	3396	OG1	THR	B 9	74.622	129.763	39.432	1.00	80.77	B	O
ATOM	3397	CG2	THR	B 9	76.205	130.082	41.236	1.00	79.47	B	C
ATOM	3398	C	THR	B 9	73.166	127.734	40.805	1.00	73.93	B	C
ATOM	3399	O	THR	B 9	73.022	126.988	39.837	1.00	73.45	B	O
ATOM	3400	N	ASN	B 10	72.147	128.216	41.503	1.00	70.73	B	N
ATOM	3401	CA	ASN	B 10	70.773	127.890	41.158	1.00	67.48	B	C
ATOM	3402	CB	ASN	B 10	70.226	126.813	42.105	1.00	69.89	B	C
ATOM	3403	CG	ASN	B 10	71.284	125.809	42.542	1.00	72.89	B	C
ATOM	3404	OD1	ASN	B 10	71.676	124.917	41.781	1.00	72.79	B	O
ATOM	3405	ND2	ASN	B 10	71.756	125.955	43.781	1.00	73.37	B	N
ATOM	3406	C	ASN	B 10	69.914	129.135	41.319	1.00	62.95	B	C
ATOM	3407	O	ASN	B 10	70.165	129.947	42.209	1.00	61.58	B	O
ATOM	3408	N	ASP	B 11	68.919	129.301	40.452	1.00	58.15	B	N
ATOM	3409	CA	ASP	B 11	68.002	130.419	40.604	1.00	52.83	B	C
ATOM	3410	CB	ASP	B 11	67.287	130.770	39.303	1.00	53.10	B	C
ATOM	3411	CG	ASP	B 11	68.231	131.117	38.184	1.00	53.83	B	C
ATOM	3412	OD1	ASP	B 11	69.236	131.822	38.429	1.00	54.14	B	O
ATOM	3413	OD2	ASP	B 11	67.950	130.691	37.045	1.00	54.59	B	O

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ATOM	3414	C	ASP	B	11	66.974	129.837	41.550	1.00	49.45	B	C
ATOM	3415	O	ASP	B	11	66.700	128.652	41.492	1.00	49.66	B	O
ATOM	3416	N	ILE	B	12	66.428	130.637	42.449	1.00	48.62	B	N
ATOM	3417	CA	ILE	B	12	65.404	130.113	43.336	1.00	46.85	B	C
ATOM	3418	CB	ILE	B	12	65.629	130.517	44.822	1.00	47.15	B	C
ATOM	3419	CG2	ILE	B	12	64.386	130.161	45.649	1.00	44.03	B	C
ATOM	3420	CG1	ILE	B	12	66.802	129.728	45.421	1.00	46.73	B	C
ATOM	3421	CD1	ILE	B	12	68.063	129.747	44.619	1.00	48.15	B	C
ATOM	3422	C	ILE	B	12	64.136	130.735	42.794	1.00	45.29	B	C
ATOM	3423	O	ILE	B	12	63.907	131.931	42.947	1.00	44.70	B	O
ATOM	3424	N	LEU	B	13	63.333	129.905	42.135	1.00	45.84	B	N
ATOM	3425	CA	LEU	B	13	62.093	130.338	41.504	1.00	44.84	B	C
ATOM	3426	CB	LEU	B	13	61.810	129.458	40.291	1.00	43.83	B	C
ATOM	3427	CG	LEU	B	13	62.955	129.365	39.291	1.00	43.13	B	C
ATOM	3428	CD1	LEU	B	13	62.576	128.415	38.165	1.00	43.07	B	C
ATOM	3429	CD2	LEU	B	13	63.257	130.751	38.751	1.00	40.30	B	C
ATOM	3430	C	LEU	B	13	60.859	130.344	42.381	1.00	45.40	B	C
ATOM	3431	O	LEU	B	13	60.833	129.756	43.456	1.00	45.47	B	O
ATOM	3432	N	PRO	B	14	59.816	131.046	41.930	1.00	48.34	B	N
ATOM	3433	CD	PRO	B	14	59.780	132.005	40.809	1.00	49.35	B	C
ATOM	3434	CA	PRO	B	14	58.577	131.099	42.699	1.00	49.81	B	C
ATOM	3435	CB	PRO	B	14	57.643	131.877	41.779	1.00	49.97	B	C
ATOM	3436	CG	PRO	B	14	58.582	132.873	41.162	1.00	50.65	B	C
ATOM	3437	C	PRO	B	14	58.122	129.664	42.923	1.00	50.80	B	C
ATOM	3438	O	PRO	B	14	58.520	128.747	42.194	1.00	52.34	B	O
ATOM	3439	N	GLY	B	15	57.293	129.456	43.930	1.00	51.19	B	N
ATOM	3440	CA	GLY	B	15	56.855	128.104	44.194	1.00	52.62	B	C
ATOM	3441	C	GLY	B	15	57.832	127.444	45.140	1.00	53.01	B	C
ATOM	3442	O	GLY	B	15	57.425	126.671	46.005	1.00	56.43	B	O
ATOM	3443	N	THR	B	16	59.118	127.741	44.989	1.00	51.43	B	N
ATOM	3444	CA	THR	B	16	60.118	127.163	45.875	1.00	49.67	B	C
ATOM	3445	CB	THR	B	16	61.145	126.311	45.073	1.00	51.42	B	C
ATOM	3446	OG1	THR	B	16	62.463	126.511	45.594	1.00	48.64	B	O
ATOM	3447	CG2	THR	B	16	61.088	126.654	43.585	1.00	54.16	B	C
ATOM	3448	C	THR	B	16	60.800	128.238	46.734	1.00	49.03	B	C
ATOM	3449	O	THR	B	16	61.345	127.953	47.804	1.00	47.08	B	O
ATOM	3450	N	SER	B	17	60.734	129.487	46.293	1.00	47.27	B	N
ATOM	3451	CA	SER	B	17	61.329	130.561	47.071	1.00	46.03	B	C
ATOM	3452	CB	SER	B	17	61.313	131.868	46.268	1.00	44.71	B	C
ATOM	3453	OG	SER	B	17	59.996	132.277	45.953	1.00	43.47	B	O
ATOM	3454	C	SER	B	17	60.583	130.726	48.408	1.00	47.22	B	C
ATOM	3455	O	SER	B	17	61.160	131.171	49.402	1.00	45.93	B	O
ATOM	3456	N	GLU	B	18	59.304	130.357	48.440	1.00	47.73	B	N
ATOM	3457	CA	GLU	B	18	58.529	130.456	49.679	1.00	49.06	B	C
ATOM	3458	CB	GLU	B	18	57.050	130.105	49.457	1.00	51.37	B	C
ATOM	3459	CG	GLU	B	18	56.267	131.074	48.600	1.00	56.38	B	C
ATOM	3460	CD	GLU	B	18	56.737	131.089	47.154	1.00	59.06	B	C
ATOM	3461	OE1	GLU	B	18	57.245	130.042	46.689	1.00	58.30	B	O
ATOM	3462	OE2	GLU	B	18	56.583	132.143	46.488	1.00	59.91	B	O
ATOM	3463	C	GLU	B	18	59.087	129.516	50.745	1.00	47.12	B	C
ATOM	3464	O	GLU	B	18	58.981	129.790	51.935	1.00	48.28	B	O
ATOM	3465	N	LYS	B	19	59.662	128.396	50.330	1.00	46.17	B	N
ATOM	3466	CA	LYS	B	19	60.224	127.470	51.307	1.00	46.57	B	C
ATOM	3467	CB	LYS	B	19	60.749	126.200	50.623	1.00	47.69	B	C
ATOM	3468	CG	LYS	B	19	59.660	125.403	49.901	1.00	51.03	B	C
ATOM	3469	CD	LYS	B	19	60.170	124.073	49.347	1.00	53.25	B	C
ATOM	3470	CE	LYS	B	19	59.042	123.306	48.653	1.00	55.43	B	C
ATOM	3471	NZ	LYS	B	19	59.432	121.904	48.317	1.00	57.53	B	N
ATOM	3472	C	LYS	B	19	61.354	128.205	52.013	1.00	45.93	B	C
ATOM	3473	O	LYS	B	19	61.428	128.223	53.245	1.00	45.32	B	O
ATOM	3474	N	TRP	B	20	62.224	128.823	51.221	1.00	44.51	B	N

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ATOM	3475	CA	TRP	B	20	63.335	129.589	51.765	1.00	44.46	B	C
ATOM	3476	CB	TRP	B	20	64.133	130.251	50.638	1.00	44.67	B	C
ATOM	3477	CG	TRP	B	20	64.962	129.297	49.833	1.00	44.51	B	C
ATOM	3478	CD2	TRP	B	20	66.391	129.203	49.839	1.00	45.12	B	C
ATOM	3479	CE2	TRP	B	20	66.749	128.199	48.911	1.00	43.95	B	C
ATOM	3480	CE3	TRP	B	20	67.406	129.873	50.537	1.00	44.06	B	C
ATOM	3481	CD1	TRP	B	20	64.519	128.366	48.931	1.00	44.60	B	C
ATOM	3482	NE1	TRP	B	20	65.592	127.704	48.371	1.00	43.85	B	N
ATOM	3483	CZ2	TRP	B	20	68.079	127.852	48.666	1.00	45.31	B	C
ATOM	3484	CZ3	TRP	B	20	68.724	129.528	50.293	1.00	44.61	B	C
ATOM	3485	CH2	TRP	B	20	69.051	128.526	49.365	1.00	43.59	B	C
ATOM	3486	C	TRP	B	20	62.774	130.661	52.693	1.00	43.44	B	C
ATOM	3487	O	TRP	B	20	63.251	130.847	53.817	1.00	43.72	B	O
ATOM	3488	N	GLN	B	21	61.753	131.362	52.216	1.00	41.64	B	N
ATOM	3489	CA	GLN	B	21	61.126	132.408	53.008	1.00	41.12	B	C
ATOM	3490	CB	GLN	B	21	59.967	133.032	52.242	1.00	39.88	B	C
ATOM	3491	CG	GLN	B	21	60.383	134.085	51.256	1.00	40.69	B	C
ATOM	3492	CD	GLN	B	21	59.297	134.367	50.239	1.00	43.19	B	C
ATOM	3493	OE1	GLN	B	21	58.114	134.400	50.577	1.00	47.09	B	O
ATOM	3494	NE2	GLN	B	21	59.690	134.578	48.988	1.00	42.88	B	N
ATOM	3495	C	GLN	B	21	60.620	131.858	54.330	1.00	40.29	B	C
ATOM	3496	O	GLN	B	21	60.713	132.521	55.357	1.00	38.21	B	O
ATOM	3497	N	PHE	B	22	60.075	130.647	54.300	1.00	41.85	B	N
ATOM	3498	CA	PHE	B	22	59.563	130.036	55.517	1.00	41.83	B	C
ATOM	3499	CB	PHE	B	22	58.805	128.750	55.199	1.00	42.82	B	C
ATOM	3500	CG	PHE	B	22	58.362	127.997	56.420	1.00	43.84	B	C
ATOM	3501	CD1	PHE	B	22	57.413	128.539	57.280	1.00	44.48	B	C
ATOM	3502	CD2	PHE	B	22	58.904	126.751	56.718	1.00	43.12	B	C
ATOM	3503	CE1	PHE	B	22	57.007	127.844	58.428	1.00	45.79	B	C
ATOM	3504	CE2	PHE	B	22	58.509	126.052	57.854	1.00	44.62	B	C
ATOM	3505	CZ	PHE	B	22	57.558	126.598	58.713	1.00	45.62	B	C
ATOM	3506	C	PHE	B	22	60.703	129.727	56.484	1.00	41.79	B	C
ATOM	3507	O	PHE	B	22	60.641	130.059	57.666	1.00	42.80	B	O
ATOM	3508	N	VAL	B	23	61.747	129.087	55.986	1.00	40.95	B	N
ATOM	3509	CA	VAL	B	23	62.872	128.758	56.841	1.00	41.33	B	C
ATOM	3510	CB	VAL	B	23	63.981	128.088	56.039	1.00	42.12	B	C
ATOM	3511	CG1	VAL	B	23	65.182	127.819	56.937	1.00	41.26	B	C
ATOM	3512	CG2	VAL	B	23	63.451	126.796	55.434	1.00	44.08	B	C
ATOM	3513	C	VAL	B	23	63.430	130.016	57.487	1.00	40.11	B	C
ATOM	3514	O	VAL	B	23	63.620	130.084	58.701	1.00	38.32	B	O
ATOM	3515	N	GLU	B	24	63.684	131.009	56.646	1.00	40.96	B	N
ATOM	3516	CA	GLU	B	24	64.237	132.285	57.069	1.00	39.81	B	C
ATOM	3517	CB	GLU	B	24	64.433	133.180	55.833	1.00	40.35	B	C
ATOM	3518	CG	GLU	B	24	65.651	132.777	54.986	1.00	38.65	B	C
ATOM	3519	CD	GLU	B	24	65.585	133.222	53.524	1.00	38.76	B	C
ATOM	3520	OE1	GLU	B	24	64.732	134.065	53.167	1.00	35.38	B	O
ATOM	3521	OE2	GLU	B	24	66.417	132.723	52.727	1.00	40.18	B	O
ATOM	3522	C	GLU	B	24	63.370	132.980	58.111	1.00	40.97	B	C
ATOM	3523	O	GLU	B	24	63.875	133.515	59.094	1.00	38.20	B	O
ATOM	3524	N	GLU	B	25	62.059	132.955	57.898	1.00	42.60	B	N
ATOM	3525	CA	GLU	B	25	61.121	133.592	58.809	1.00	44.63	B	C
ATOM	3526	CB	GLU	B	25	59.731	133.625	58.162	1.00	48.67	B	C
ATOM	3527	CG	GLU	B	25	58.781	134.667	58.717	1.00	56.79	B	C
ATOM	3528	CD	GLU	B	25	57.614	134.949	57.767	1.00	64.52	B	C
ATOM	3529	OE1	GLU	B	25	57.868	135.385	56.610	1.00	65.43	B	O
ATOM	3530	OE2	GLU	B	25	56.446	134.735	58.178	1.00	66.26	B	O
ATOM	3531	C	GLU	B	25	61.078	132.845	60.145	1.00	42.34	B	C
ATOM	3532	O	GLU	B	25	60.913	133.443	61.204	1.00	40.87	B	O
ATOM	3533	N	THR	B	26	61.233	131.533	60.096	1.00	41.73	B	N
ATOM	3534	CA	THR	B	26	61.204	130.751	61.316	1.00	40.89	B	C
ATOM	3535	CB	THR	B	26	61.153	129.259	60.996	1.00	40.75	B	C

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ATOM	3536	OG1	THR	B	26	59.950	128.993	60.264	1.00	40.41	B	O
ATOM	3537	CG2	THR	B	26	61.169	128.422	62.282	1.00	36.39	B	C
ATOM	3538	C	THR	B	26	62.426	131.081	62.170	1.00	41.65	B	C
ATOM	3539	O	THR	B	26	62.307	131.289	63.381	1.00	42.81	B	O
ATOM	3540	N	ALA	B	27	63.594	131.145	61.543	1.00	39.93	B	N
ATOM	3541	CA	ALA	B	27	64.807	131.479	62.273	1.00	40.38	B	C
ATOM	3542	CB	ALA	B	27	66.010	131.435	61.345	1.00	41.16	B	C
ATOM	3543	C	ALA	B	27	64.666	132.872	62.888	1.00	41.12	B	C
ATOM	3544	O	ALA	B	27	64.825	133.034	64.100	1.00	40.95	B	O
ATOM	3545	N	ARG	B	28	64.342	133.871	62.065	1.00	41.32	B	N
ATOM	3546	CA	ARG	B	28	64.190	135.240	62.558	1.00	41.96	B	C
ATOM	3547	CB	ARG	B	28	63.667	136.169	61.460	1.00	45.52	B	C
ATOM	3548	CG	ARG	B	28	64.662	136.479	60.376	1.00	47.44	B	C
ATOM	3549	CD	ARG	B	28	64.207	137.672	59.548	1.00	52.20	B	C
ATOM	3550	NE	ARG	B	28	64.278	137.399	58.111	1.00	54.70	B	N
ATOM	3551	CZ	ARG	B	28	63.255	136.958	57.382	1.00	52.91	B	C
ATOM	3552	NH1	ARG	B	28	62.075	136.744	57.946	1.00	53.20	B	N
ATOM	3553	NH2	ARG	B	28	63.413	136.727	56.086	1.00	54.10	B	N
ATOM	3554	C	ARG	B	28	63.280	135.381	63.775	1.00	42.15	B	C
ATOM	3555	O	ARG	B	28	63.541	136.199	64.653	1.00	40.17	B	O
ATOM	3556	N	LEU	B	29	62.207	134.599	63.818	1.00	43.81	B	N
ATOM	3557	CA	LEU	B	29	61.271	134.660	64.933	1.00	46.45	B	C
ATOM	3558	CB	LEU	B	29	59.963	133.952	64.567	1.00	48.47	B	C
ATOM	3559	CG	LEU	B	29	59.108	134.649	63.500	1.00	51.20	B	C
ATOM	3560	CD1	LEU	B	29	57.987	133.727	63.023	1.00	51.71	B	C
ATOM	3561	CD2	LEU	B	29	58.529	135.919	64.084	1.00	52.77	B	C
ATOM	3562	C	LEU	B	29	61.852	134.044	66.201	1.00	46.65	B	C
ATOM	3563	O	LEU	B	29	61.787	134.641	67.272	1.00	47.61	B	O
ATOM	3564	N	ILE	B	30	62.416	132.849	66.081	1.00	46.75	B	N
ATOM	3565	CA	ILE	B	30	62.998	132.177	67.234	1.00	45.59	B	C
ATOM	3566	CB	ILE	B	30	63.587	130.811	66.839	1.00	46.40	B	C
ATOM	3567	CG2	ILE	B	30	63.915	130.020	68.078	1.00	48.00	B	C
ATOM	3568	CG1	ILE	B	30	62.575	130.015	66.008	1.00	51.50	B	C
ATOM	3569	CD1	ILE	B	30	61.311	129.595	66.760	1.00	52.35	B	C
ATOM	3570	C	ILE	B	30	64.115	133.054	67.812	1.00	44.25	B	C
ATOM	3571	O	ILE	B	30	64.123	133.373	69.004	1.00	43.02	B	O
ATOM	3572	N	PHE	B	31	65.042	133.453	66.948	1.00	41.44	B	N
ATOM	3573	CA	PHE	B	31	66.168	134.279	67.351	1.00	41.96	B	C
ATOM	3574	CB	PHE	B	31	67.014	134.622	66.124	1.00	39.57	B	C
ATOM	3575	CG	PHE	B	31	67.729	133.439	65.534	1.00	35.70	B	C
ATOM	3576	CD1	PHE	B	31	68.142	133.448	64.209	1.00	35.38	B	C
ATOM	3577	CD2	PHE	B	31	67.999	132.318	66.306	1.00	39.02	B	C
ATOM	3578	CE1	PHE	B	31	68.813	132.357	63.658	1.00	32.01	B	C
ATOM	3579	CE2	PHE	B	31	68.670	131.220	65.765	1.00	38.15	B	C
ATOM	3580	CZ	PHE	B	31	69.075	131.249	64.430	1.00	36.29	B	C
ATOM	3581	C	PHE	B	31	65.731	135.548	68.078	1.00	42.67	B	C
ATOM	3582	O	PHE	B	31	66.320	135.925	69.093	1.00	41.37	B	O
ATOM	3583	N	LYS	B	32	64.701	136.205	67.558	1.00	43.80	B	N
ATOM	3584	CA	LYS	B	32	64.187	137.409	68.189	1.00	45.35	B	C
ATOM	3585	CB	LYS	B	32	63.049	137.998	67.347	1.00	48.33	B	C
ATOM	3586	CG	LYS	B	32	62.295	139.136	68.021	1.00	53.31	B	C
ATOM	3587	CD	LYS	B	32	61.233	139.757	67.119	1.00	55.54	B	C
ATOM	3588	CE	LYS	B	32	61.852	140.715	66.110	1.00	59.24	B	C
ATOM	3589	NZ	LYS	B	32	60.814	141.493	65.362	1.00	62.54	B	N
ATOM	3590	C	LYS	B	32	63.694	137.074	69.606	1.00	44.54	B	C
ATOM	3591	O	LYS	B	32	63.903	137.854	70.541	1.00	41.86	B	O
ATOM	3592	N	ASP	B	33	63.058	135.912	69.758	1.00	43.89	B	N
ATOM	3593	CA	ASP	B	33	62.552	135.474	71.059	1.00	44.95	B	C
ATOM	3594	CB	ASP	B	33	61.753	134.171	70.928	1.00	48.90	B	C
ATOM	3595	CG	ASP	B	33	60.317	134.401	70.459	1.00	53.38	B	C
ATOM	3596	OD1	ASP	B	33	59.634	135.280	71.033	1.00	54.51	B	O

FIGURE 11-69

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ATOM	3597	OD2	ASP	B	33	59.868	133.694	69.524	1.00	55.81	B	O
ATOM	3598	C	ASP	B	33	63.675	135.260	72.072	1.00	44.75	B	C
ATOM	3599	O	ASP	B	33	63.549	135.637	73.239	1.00	45.21	B	O
ATOM	3600	N	TYR	B	34	64.767	134.647	71.626	1.00	41.25	B	N
ATOM	3601	CA	TYR	B	34	65.901	134.391	72.492	1.00	38.65	B	C
ATOM	3602	CB	TYR	B	34	66.709	133.217	71.949	1.00	39.87	B	C
ATOM	3603	CG	TYR	B	34	66.110	131.861	72.247	1.00	39.26	B	C
ATOM	3604	CD1	TYR	B	34	66.628	131.060	73.266	1.00	39.45	B	C
ATOM	3605	CE1	TYR	B	34	66.124	129.781	73.513	1.00	37.93	B	C
ATOM	3606	CD2	TYR	B	34	65.059	131.357	71.481	1.00	40.52	B	C
ATOM	3607	CE2	TYR	B	34	64.548	130.085	71.714	1.00	40.09	B	C
ATOM	3608	CZ	TYR	B	34	65.087	129.297	72.733	1.00	40.78	B	C
ATOM	3609	OH	TYR	B	34	64.599	128.024	72.949	1.00	38.74	B	O
ATOM	3610	C	TYR	B	34	66.811	135.608	72.648	1.00	38.39	B	C
ATOM	3611	O	TYR	B	34	67.918	135.496	73.160	1.00	36.98	B	O
ATOM	3612	N	GLN	B	35	66.339	136.765	72.193	1.00	36.97	B	N
ATOM	3613	CA	GLN	B	35	67.079	138.016	72.285	1.00	37.14	B	C
ATOM	3614	CB	GLN	B	35	67.507	138.291	73.731	1.00	38.45	B	C
ATOM	3615	CG	GLN	B	35	66.404	138.183	74.775	1.00	38.16	B	C
ATOM	3616	CD	GLN	B	35	65.114	138.859	74.347	1.00	39.93	B	C
ATOM	3617	OE1	GLN	B	35	65.071	140.069	74.120	1.00	40.08	B	O
ATOM	3618	NE2	GLN	B	35	64.051	138.069	74.226	1.00	39.21	B	N
ATOM	3619	C	GLN	B	35	68.299	138.161	71.379	1.00	38.41	B	C
ATOM	3620	O	GLN	B	35	69.271	138.803	71.758	1.00	39.85	B	O
ATOM	3621	N	TYR	B	36	68.257	137.570	70.190	1.00	40.13	B	N
ATOM	3622	CA	TYR	B	36	69.355	137.702	69.233	1.00	40.33	B	C
ATOM	3623	CB	TYR	B	36	69.608	136.384	68.518	1.00	41.63	B	C
ATOM	3624	CG	TYR	B	36	70.345	135.383	69.363	1.00	43.86	B	C
ATOM	3625	CD1	TYR	B	36	71.669	135.062	69.093	1.00	42.52	B	C
ATOM	3626	CE1	TYR	B	36	72.353	134.151	69.883	1.00	43.50	B	C
ATOM	3627	CD2	TYR	B	36	69.724	134.768	70.447	1.00	43.74	B	C
ATOM	3628	CE2	TYR	B	36	70.404	133.858	71.239	1.00	42.76	B	C
ATOM	3629	CZ	TYR	B	36	71.712	133.555	70.949	1.00	41.04	B	C
ATOM	3630	OH	TYR	B	36	72.378	132.637	71.707	1.00	40.50	B	O
ATOM	3631	C	TYR	B	36	68.974	138.758	68.206	1.00	41.26	B	C
ATOM	3632	O	TYR	B	36	67.818	138.832	67.788	1.00	41.62	B	O
ATOM	3633	N	GLN	B	37	69.942	139.576	67.801	1.00	41.39	B	N
ATOM	3634	CA	GLN	B	37	69.679	140.622	66.825	1.00	40.00	B	C
ATOM	3635	CB	GLN	B	37	69.965	142.000	67.428	1.00	43.43	B	C
ATOM	3636	CG	GLN	B	37	69.232	142.256	68.735	1.00	45.38	B	C
ATOM	3637	CD	GLN	B	37	68.489	143.565	68.735	1.00	46.08	B	C
ATOM	3638	OE1	GLN	B	37	69.081	144.630	68.615	1.00	47.91	B	O
ATOM	3639	NE2	GLN	B	37	67.175	143.492	68.870	1.00	50.85	B	N
ATOM	3640	C	GLN	B	37	70.536	140.404	65.597	1.00	39.54	B	C
ATOM	3641	O	GLN	B	37	71.701	140.023	65.697	1.00	39.28	B	O
ATOM	3642	N	GLU	B	38	69.954	140.659	64.432	1.00	39.60	B	N
ATOM	3643	CA	GLU	B	38	70.657	140.457	63.182	1.00	37.32	B	C
ATOM	3644	CB	GLU	B	38	69.687	140.483	61.987	1.00	36.73	B	C
ATOM	3645	CG	GLU	B	38	70.406	140.252	60.656	1.00	39.01	B	C
ATOM	3646	CD	GLU	B	38	69.484	140.177	59.444	1.00	39.98	B	C
ATOM	3647	OE1	GLU	B	38	68.429	140.835	59.449	1.00	39.97	B	O
ATOM	3648	OE2	GLU	B	38	69.834	139.479	58.469	1.00	41.19	B	O
ATOM	3649	C	GLU	B	38	71.802	141.414	62.912	1.00	37.12	B	C
ATOM	3650	O	GLU	B	38	71.780	142.600	63.263	1.00	34.84	B	O
ATOM	3651	N	ILE	B	39	72.816	140.865	62.265	1.00	35.68	B	N
ATOM	3652	CA	ILE	B	39	73.977	141.630	61.897	1.00	36.70	B	C
ATOM	3653	CB	ILE	B	39	75.147	141.287	62.802	1.00	35.29	B	C
ATOM	3654	CG2	ILE	B	39	75.443	139.795	62.726	1.00	40.43	B	C
ATOM	3655	CG1	ILE	B	39	76.366	142.093	62.403	1.00	37.13	B	C
ATOM	3656	CD1	ILE	B	39	77.517	141.880	63.354	1.00	41.30	B	C
ATOM	3657	C	ILE	B	39	74.262	141.232	60.458	1.00	35.92	B	C

FIGURE 11-70

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ATOM	3658	O	ILE	B	39	74.238	140.045	60.114	1.00	34.86	B	O
ATOM	3659	N	ARG	B	40	74.483	142.224	59.605	1.00	34.95	B	N
ATOM	3660	CA	ARG	B	40	74.769	141.939	58.217	1.00	36.81	B	C
ATOM	3661	CB	ARG	B	40	73.672	142.501	57.308	1.00	37.88	B	C
ATOM	3662	CG	ARG	B	40	72.306	141.922	57.578	1.00	38.00	B	C
ATOM	3663	CD	ARG	B	40	71.256	142.510	56.661	1.00	38.12	B	C
ATOM	3664	NE	ARG	B	40	69.906	142.092	57.042	1.00	37.08	B	N
ATOM	3665	CZ	ARG	B	40	68.810	142.402	56.359	1.00	35.44	B	C
ATOM	3666	NH1	ARG	B	40	68.902	143.133	55.253	1.00	33.18	B	N
ATOM	3667	NH2	ARG	B	40	67.622	141.978	56.781	1.00	35.98	B	N
ATOM	3668	C	ARG	B	40	76.104	142.546	57.845	1.00	37.35	B	C
ATOM	3669	O	ARG	B	40	76.334	143.741	58.038	1.00	38.73	B	O
ATOM	3670	N	THR	B	41	76.990	141.711	57.324	1.00	37.92	B	N
ATOM	3671	CA	THR	B	41	78.302	142.174	56.898	1.00	38.52	B	C
ATOM	3672	CB	THR	B	41	79.420	141.286	57.475	1.00	38.06	B	C
ATOM	3673	OG1	THR	B	41	79.231	139.925	57.058	1.00	37.29	B	O
ATOM	3674	CG2	THR	B	41	79.392	141.347	58.988	1.00	36.32	B	C
ATOM	3675	C	THR	B	41	78.304	142.096	55.384	1.00	37.50	B	C
ATOM	3676	O	THR	B	41	77.456	141.429	54.802	1.00	37.11	B	O
ATOM	3677	N	PRO	B	42	79.244	142.783	54.726	1.00	39.02	B	N
ATOM	3678	CD	PRO	B	42	80.200	143.760	55.278	1.00	37.63	B	C
ATOM	3679	CA	PRO	B	42	79.304	142.756	53.258	1.00	39.15	B	C
ATOM	3680	CB	PRO	B	42	80.439	143.719	52.942	1.00	38.64	B	C
ATOM	3681	CG	PRO	B	42	80.414	144.684	54.105	1.00	38.63	B	C
ATOM	3682	C	PRO	B	42	79.564	141.364	52.685	1.00	42.12	B	C
ATOM	3683	O	PRO	B	42	80.135	140.498	53.348	1.00	42.56	B	O
ATOM	3684	N	ILE	B	43	79.122	141.148	51.454	1.00	45.66	B	N
ATOM	3685	CA	ILE	B	43	79.344	139.873	50.787	1.00	49.13	B	C
ATOM	3686	CB	ILE	B	43	78.656	139.831	49.408	1.00	49.53	B	C
ATOM	3687	CG2	ILE	B	43	78.991	138.533	48.707	1.00	50.93	B	C
ATOM	3688	CG1	ILE	B	43	77.141	140.013	49.566	1.00	47.56	B	C
ATOM	3689	CD1	ILE	B	43	76.484	138.964	50.403	1.00	44.35	B	C
ATOM	3690	C	ILE	B	43	80.850	139.757	50.590	1.00	51.35	B	C
ATOM	3691	O	ILE	B	43	81.412	138.670	50.634	1.00	51.70	B	O
ATOM	3692	N	PHE	B	44	81.500	140.894	50.369	1.00	56.27	B	N
ATOM	3693	CA	PHE	B	44	82.942	140.913	50.198	1.00	62.22	B	C
ATOM	3694	CB	PHE	B	44	83.332	141.820	49.039	1.00	64.85	B	C
ATOM	3695	CG	PHE	B	44	83.095	141.198	47.702	1.00	69.63	B	C
ATOM	3696	CD1	PHE	B	44	81.843	141.262	47.102	1.00	71.08	B	C
ATOM	3697	CD2	PHE	B	44	84.115	140.495	47.060	1.00	72.03	B	C
ATOM	3698	CE1	PHE	B	44	81.606	140.631	45.878	1.00	73.57	B	C
ATOM	3699	CE2	PHE	B	44	83.891	139.860	45.834	1.00	73.48	B	C
ATOM	3700	CZ	PHE	B	44	82.633	139.929	45.243	1.00	73.69	B	C
ATOM	3701	C	PHE	B	44	83.612	141.370	51.478	1.00	64.64	B	C
ATOM	3702	O	PHE	B	44	83.374	142.476	51.956	1.00	65.91	B	O
ATOM	3703	N	GLU	B	45	84.450	140.501	52.031	1.00	67.89	B	N
ATOM	3704	CA	GLU	B	45	85.145	140.780	53.279	1.00	71.76	B	C
ATOM	3705	CB	GLU	B	45	84.960	139.585	54.221	1.00	70.54	B	C
ATOM	3706	CG	GLU	B	45	85.375	139.839	55.655	1.00	71.65	B	C
ATOM	3707	CD	GLU	B	45	84.476	140.839	56.367	1.00	72.14	B	C
ATOM	3708	OE1	GLU	B	45	84.796	141.181	57.520	1.00	74.74	B	O
ATOM	3709	OE2	GLU	B	45	83.456	141.282	55.792	1.00	70.07	B	O
ATOM	3710	C	GLU	B	45	86.635	141.055	53.060	1.00	75.16	B	C
ATOM	3711	O	GLU	B	45	87.185	140.724	52.010	1.00	75.00	B	O
ATOM	3712	N	HIS	B	46	87.279	141.673	54.049	1.00	80.43	B	N
ATOM	3713	CA	HIS	B	46	88.711	141.967	53.970	1.00	85.56	B	C
ATOM	3714	CB	HIS	B	46	89.199	142.688	55.234	1.00	88.12	B	C
ATOM	3715	CG	HIS	B	46	88.700	144.093	55.379	1.00	91.13	B	C
ATOM	3716	CD2	HIS	B	46	88.002	144.691	56.376	1.00	92.15	B	C
ATOM	3717	ND1	HIS	B	46	88.959	145.078	54.449	1.00	91.82	B	N
ATOM	3718	CE1	HIS	B	46	88.443	146.221	54.867	1.00	92.65	B	C

FIGURE 11-71

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ATOM	3719	NE2	HIS	B	46	87.858	146.014	56.034	1.00	93.14	B	N
ATOM	3720	C	HIS	B	46	89.465	140.643	53.852	1.00	88.10	B	C
ATOM	3721	O	HIS	B	46	89.232	139.716	54.634	1.00	87.88	B	O
ATOM	3722	N	TYR	B	47	90.370	140.559	52.882	1.00	90.87	B	N
ATOM	3723	CA	TYR	B	47	91.156	139.347	52.668	1.00	93.57	B	C
ATOM	3724	CB	TYR	B	47	92.252	139.617	51.627	1.00	95.73	B	C
ATOM	3725	CG	TYR	B	47	93.309	138.534	51.535	1.00	97.90	B	C
ATOM	3726	CD1	TYR	B	47	92.989	137.249	51.096	1.00	98.53	B	C
ATOM	3727	CE1	TYR	B	47	93.956	136.246	51.042	1.00	99.43	B	C
ATOM	3728	CD2	TYR	B	47	94.627	138.792	51.917	1.00	99.02	B	C
ATOM	3729	CE2	TYR	B	47	95.599	137.800	51.869	1.00	99.60	B	C
ATOM	3730	CZ	TYR	B	47	95.260	136.530	51.432	1.00100.00	B	C	
ATOM	3731	OH	TYR	B	47	96.229	135.550	51.390	1.00100.00	B	O	
ATOM	3732	C	TYR	B	47	91.780	138.815	53.963	1.00	94.28	B	C
ATOM	3733	O	TYR	B	47	91.694	137.619	54.258	1.00	94.11	B	O
ATOM	3734	N	GLU	B	48	92.403	139.708	54.731	1.00	95.41	B	N
ATOM	3735	CA	GLU	B	48	93.049	139.337	55.991	1.00	96.05	B	C
ATOM	3736	CB	GLU	B	48	93.678	140.567	56.662	1.00	97.16	B	C
ATOM	3737	CG	GLU	B	48	94.817	141.230	55.889	1.00	98.90	B	C
ATOM	3738	CD	GLU	B	48	94.336	142.205	54.825	1.00	99.92	B	C
ATOM	3739	OE1	GLU	B	48	93.740	141.762	53.819	1.00	99.70	B	O
ATOM	3740	OE2	GLU	B	48	94.555	143.424	55.001	1.00100.00	B	O	
ATOM	3741	C	GLU	B	48	92.085	138.676	56.975	1.00	95.57	B	C
ATOM	3742	O	GLU	B	48	92.383	137.618	57.530	1.00	95.94	B	O
ATOM	3743	N	VAL	B	49	90.936	139.310	57.194	1.00	94.49	B	N
ATOM	3744	CA	VAL	B	49	89.927	138.793	58.114	1.00	94.23	B	C
ATOM	3745	CB	VAL	B	49	88.551	139.456	57.854	1.00	93.94	B	C
ATOM	3746	CG1	VAL	B	49	87.476	138.791	58.707	1.00	92.62	B	C
ATOM	3747	CG2	VAL	B	49	88.627	140.944	58.163	1.00	92.82	B	C
ATOM	3748	C	VAL	B	49	89.758	137.274	58.028	1.00	94.19	B	C
ATOM	3749	O	VAL	B	49	89.682	136.593	59.054	1.00	94.00	B	O
ATOM	3750	N	ILE	B	50	89.700	136.755	56.804	1.00	93.93	B	N
ATOM	3751	CA	ILE	B	50	89.530	135.321	56.571	1.00	93.80	B	C
ATOM	3752	CB	ILE	B	50	89.494	135.012	55.048	1.00	93.12	B	C
ATOM	3753	CG2	ILE	B	50	89.172	133.538	54.816	1.00	91.54	B	C
ATOM	3754	CG1	ILE	B	50	88.451	135.904	54.360	1.00	92.30	B	C
ATOM	3755	CD1	ILE	B	50	87.044	135.798	54.937	1.00	90.73	B	C
ATOM	3756	C	ILE	B	50	90.634	134.489	57.238	1.00	94.39	B	C
ATOM	3757	O	ILE	B	50	90.345	133.624	58.071	1.00	93.84	B	O
ATOM	3758	N	SER	B	51	91.888	134.757	56.871	1.00	94.53	B	N
ATOM	3759	CA	SER	B	51	93.046	134.052	57.432	1.00	95.15	B	C
ATOM	3760	CB	SER	B	51	93.167	134.342	58.933	1.00	95.60	B	C
ATOM	3761	OG	SER	B	51	93.332	135.727	59.186	1.00	96.13	B	O
ATOM	3762	C	SER	B	51	93.015	132.535	57.216	1.00	95.67	B	C
ATOM	3763	O	SER	B	51	93.920	132.026	56.518	1.00	95.72	B	O
ATOM	3764	OXT	SER	B	51	92.099	131.867	57.749	1.00	95.60	B	O
TER	3765		SER	B	51						B	
ATOM	3766	CB	ASP	B	70	88.202	129.707	51.421	1.00	98.67	B	C
ATOM	3767	CG	ASP	B	70	89.245	130.770	51.754	1.00	98.28	B	C
ATOM	3768	OD1	ASP	B	70	88.875	131.957	51.875	1.00	97.53	B	O
ATOM	3769	OD2	ASP	B	70	90.437	130.415	51.893	1.00	96.77	B	O
ATOM	3770	C	ASP	B	70	88.591	130.166	48.995	1.00	99.95	B	C
ATOM	3771	O	ASP	B	70	89.434	129.296	48.768	1.00100.00	B	O	
ATOM	3772	N	ASP	B	70	86.620	128.806	49.729	1.00	98.42	B	N
ATOM	3773	CA	ASP	B	70	87.522	129.949	50.066	1.00	99.32	B	C
ATOM	3774	N	LYS	B	71	88.542	131.333	48.351	1.00100.00	B	N	
ATOM	3775	CA	LYS	B	71	89.488	131.733	47.304	1.00100.00	B	C	
ATOM	3776	CB	LYS	B	71	89.808	130.563	46.359	1.00100.00	B	C	
ATOM	3777	CG	LYS	B	71	91.153	129.889	46.645	1.00	99.99	B	C
ATOM	3778	CD	LYS	B	71	91.381	128.661	45.774	1.00	99.48	B	C
ATOM	3779	CE	LYS	B	71	90.363	127.570	46.077	1.00	98.95	B	C

FIGURE 11-72

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ATOM	3780	NZ	LYS	B	71	90.615	126.333	45.286	1.00	98.69	B	N
ATOM	3781	C	LYS	B	71	88.917	132.901	46.503	1.00	100.00	B	C
ATOM	3782	O	LYS	B	71	87.701	133.093	46.457	1.00	100.00	B	O
ATOM	3783	N	GLY	B	72	89.801	133.681	45.883	1.00	100.00	B	N
ATOM	3784	CA	GLY	B	72	89.366	134.825	45.098	1.00	100.00	B	C
ATOM	3785	C	GLY	B	72	90.456	135.853	44.829	1.00	100.00	B	C
ATOM	3786	O	GLY	B	72	91.388	135.592	44.062	1.00	100.00	B	O
ATOM	3787	N	ASP	B	73	90.340	137.021	45.464	1.00	100.00	B	N
ATOM	3788	CA	ASP	B	73	91.301	138.116	45.295	1.00	100.00	B	C
ATOM	3789	CB	ASP	B	73	90.557	139.449	45.098	1.00	100.00	B	C
ATOM	3790	CG	ASP	B	73	89.699	139.472	43.843	1.00	100.00	B	C
ATOM	3791	OD1	ASP	B	73	90.265	139.373	42.734	1.00	100.00	B	O
ATOM	3792	OD2	ASP	B	73	88.459	139.597	43.966	1.00	100.00	B	O
ATOM	3793	C	ASP	B	73	92.259	138.268	46.484	1.00	100.00	B	C
ATOM	3794	O	ASP	B	73	92.402	137.361	47.308	1.00	100.00	B	O
ATOM	3795	N	ARG	B	74	92.910	139.431	46.549	1.00	100.00	B	N
ATOM	3796	CA	ARG	B	74	93.845	139.769	47.624	1.00	99.63	B	C
ATOM	3797	CB	ARG	B	74	95.277	139.918	47.083	1.00	100.00	B	C
ATOM	3798	CG	ARG	B	74	95.776	141.359	46.984	1.00	99.85	B	C
ATOM	3799	CD	ARG	B	74	97.268	141.415	46.689	1.00	99.71	B	C
ATOM	3800	NE	ARG	B	74	97.795	142.779	46.738	1.00	100.00	B	N
ATOM	3801	CZ	ARG	B	74	97.428	143.762	45.916	1.00	100.00	B	C
ATOM	3802	NH1	ARG	B	74	97.969	144.969	46.041	1.00	99.53	B	N
ATOM	3803	NH2	ARG	B	74	96.523	143.542	44.967	1.00	100.00	B	N
ATOM	3804	C	ARG	B	74	93.384	141.089	48.253	1.00	98.72	B	C
ATOM	3805	O	ARG	B	74	93.637	141.351	49.432	1.00	98.35	B	O
ATOM	3806	N	HIS	B	75	92.724	141.919	47.445	1.00	97.93	B	N
ATOM	3807	CA	HIS	B	75	92.185	143.200	47.905	1.00	96.85	B	C
ATOM	3808	CB	HIS	B	75	91.672	144.038	46.720	1.00	98.10	B	C
ATOM	3809	CG	HIS	B	75	92.727	144.863	46.044	1.00	99.70	B	C
ATOM	3810	CD2	HIS	B	75	93.164	144.874	44.761	1.00	100.00	B	C
ATOM	3811	ND1	HIS	B	75	93.435	145.851	46.696	1.00	100.00	B	N
ATOM	3812	CE1	HIS	B	75	94.260	146.435	45.846	1.00	100.00	B	C
ATOM	3813	NE2	HIS	B	75	94.115	145.861	44.664	1.00	100.00	B	N
ATOM	3814	C	HIS	B	75	91.014	142.880	48.835	1.00	94.76	B	C
ATOM	3815	O	HIS	B	75	91.016	143.246	50.010	1.00	95.29	B	O
ATOM	3816	N	VAL	B	76	90.018	142.188	48.284	1.00	91.72	B	N
ATOM	3817	CA	VAL	B	76	88.824	141.780	49.023	1.00	88.36	B	C
ATOM	3818	CB	VAL	B	76	87.663	142.787	48.829	1.00	88.91	B	C
ATOM	3819	CG1	VAL	B	76	86.567	142.514	49.840	1.00	88.93	B	C
ATOM	3820	CG2	VAL	B	76	88.172	144.214	48.965	1.00	89.60	B	C
ATOM	3821	C	VAL	B	76	88.398	140.427	48.453	1.00	85.46	B	C
ATOM	3822	O	VAL	B	76	88.726	140.113	47.308	1.00	85.12	B	O
ATOM	3823	N	THR	B	77	87.674	139.628	49.235	1.00	82.01	B	N
ATOM	3824	CA	THR	B	77	87.237	138.313	48.762	1.00	79.07	B	C
ATOM	3825	CB	THR	B	77	88.239	137.211	49.173	1.00	79.46	B	C
ATOM	3826	OG1	THR	B	77	89.525	137.495	48.610	1.00	80.63	B	O
ATOM	3827	CG2	THR	B	77	87.767	135.849	48.678	1.00	79.41	B	C
ATOM	3828	C	THR	B	77	85.862	137.889	49.265	1.00	76.15	B	C
ATOM	3829	O	THR	B	77	85.446	138.260	50.358	1.00	75.45	B	O
ATOM	3830	N	LEU	B	78	85.163	137.100	48.456	1.00	73.23	B	N
ATOM	3831	CA	LEU	B	78	83.846	136.604	48.830	1.00	70.68	B	C
ATOM	3832	CB	LEU	B	78	83.294	135.693	47.731	1.00	71.04	B	C
ATOM	3833	CG	LEU	B	78	82.883	136.408	46.441	1.00	71.77	B	C
ATOM	3834	CD1	LEU	B	78	82.607	135.387	45.341	1.00	71.48	B	C
ATOM	3835	CD2	LEU	B	78	81.649	137.269	46.708	1.00	72.36	B	C
ATOM	3836	C	LEU	B	78	83.959	135.836	50.141	1.00	67.98	B	C
ATOM	3837	O	LEU	B	78	84.817	134.969	50.291	1.00	67.45	B	O
ATOM	3838	N	ARG	B	79	83.089	136.164	51.089	1.00	66.02	B	N
ATOM	3839	CA	ARG	B	79	83.107	135.516	52.394	1.00	63.95	B	C
ATOM	3840	CB	ARG	B	79	82.136	136.221	53.353	1.00	63.98	B	C

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ATOM	3841	CG	ARG	B	79	80.669	136.110	52.963	1.00	62.44	B	C
ATOM	3842	CD	ARG	B	79	79.767	136.957	53.861	1.00	62.22	B	C
ATOM	3843	NE	ARG	B	79	78.352	136.788	53.524	1.00	59.93	B	N
ATOM	3844	CZ	ARG	B	79	77.398	137.660	53.838	1.00	58.06	B	C
ATOM	3845	NH1	ARG	B	79	77.704	138.769	54.498	1.00	56.37	B	N
ATOM	3846	NH2	ARG	B	79	76.139	137.424	53.487	1.00	54.80	B	N
ATOM	3847	C	ARG	B	79	82.763	134.035	52.313	1.00	61.90	B	C
ATOM	3848	O	ARG	B	79	81.730	133.650	51.768	1.00	59.93	B	O
ATOM	3849	N	PRO	B	80	83.647	133.178	52.835	1.00	60.78	B	N
ATOM	3850	CD	PRO	B	80	85.052	133.446	53.193	1.00	60.27	B	C
ATOM	3851	CA	PRO	B	80	83.379	131.739	52.801	1.00	60.19	B	C
ATOM	3852	CB	PRO	B	80	84.768	131.124	52.951	1.00	60.52	B	C
ATOM	3853	CG	PRO	B	80	85.490	132.130	53.795	1.00	60.20	B	C
ATOM	3854	C	PRO	B	80	82.451	131.342	53.938	1.00	59.13	B	C
ATOM	3855	O	PRO	B	80	81.785	130.310	53.880	1.00	59.24	B	O
ATOM	3856	N	GLU	B	81	82.406	132.181	54.967	1.00	57.59	B	N
ATOM	3857	CA	GLU	B	81	81.579	131.914	56.136	1.00	56.30	B	C
ATOM	3858	CB	GLU	B	81	82.370	131.081	57.133	1.00	57.60	B	C
ATOM	3859	CG	GLU	B	81	83.725	131.677	57.453	1.00	60.47	B	C
ATOM	3860	CD	GLU	B	81	84.215	131.259	58.814	1.00	63.05	B	C
ATOM	3861	OE1	GLU	B	81	84.119	130.053	59.128	1.00	64.42	B	O
ATOM	3862	OE2	GLU	B	81	84.694	132.132	59.569	1.00	65.53	B	O
ATOM	3863	C	GLU	B	81	81.117	133.212	56.799	1.00	53.75	B	C
ATOM	3864	O	GLU	B	81	81.443	134.296	56.330	1.00	54.57	B	O
ATOM	3865	N	GLY	B	82	80.364	133.094	57.891	1.00	51.84	B	N
ATOM	3866	CA	GLY	B	82	79.849	134.271	58.571	1.00	50.04	B	C
ATOM	3867	C	GLY	B	82	80.447	134.607	59.931	1.00	47.49	B	C
ATOM	3868	O	GLY	B	82	80.377	135.758	60.363	1.00	49.58	B	O
ATOM	3869	N	THR	B	83	81.030	133.624	60.607	1.00	45.81	B	N
ATOM	3870	CA	THR	B	83	81.625	133.864	61.916	1.00	43.31	B	C
ATOM	3871	CB	THR	B	83	82.159	132.549	62.539	1.00	44.70	B	C
ATOM	3872	OG1	THR	B	83	81.106	131.578	62.570	1.00	44.67	B	O
ATOM	3873	CG2	THR	B	83	82.631	132.776	63.972	1.00	43.25	B	C
ATOM	3874	C	THR	B	83	82.750	134.898	61.828	1.00	43.33	B	C
ATOM	3875	O	THR	B	83	82.660	135.958	62.455	1.00	42.71	B	O
ATOM	3876	N	ALA	B	84	83.791	134.619	61.044	1.00	40.93	B	N
ATOM	3877	CA	ALA	B	84	84.905	135.563	60.912	1.00	41.24	B	C
ATOM	3878	CB	ALA	B	84	85.870	135.123	59.792	1.00	40.63	B	C
ATOM	3879	C	ALA	B	84	84.418	136.988	60.647	1.00	40.11	B	C
ATOM	3880	O	ALA	B	84	84.848	137.933	61.310	1.00	42.44	B	O
ATOM	3881	N	PRO	B	85	83.528	137.167	59.661	1.00	38.25	B	N
ATOM	3882	CD	PRO	B	85	83.059	136.202	58.651	1.00	37.44	B	C
ATOM	3883	CA	PRO	B	85	83.023	138.510	59.369	1.00	35.84	B	C
ATOM	3884	CB	PRO	B	85	82.085	138.279	58.187	1.00	35.16	B	C
ATOM	3885	CG	PRO	B	85	82.707	137.107	57.494	1.00	35.26	B	C
ATOM	3886	C	PRO	B	85	82.274	139.073	60.570	1.00	34.51	B	C
ATOM	3887	O	PRO	B	85	82.295	140.264	60.826	1.00	33.80	B	O
ATOM	3888	N	ILE	B	86	81.605	138.216	61.321	1.00	34.43	B	N
ATOM	3889	CA	ILE	B	86	80.866	138.726	62.450	1.00	36.14	B	C
ATOM	3890	CB	ILE	B	86	79.751	137.749	62.848	1.00	37.02	B	C
ATOM	3891	CG2	ILE	B	86	79.309	137.989	64.286	1.00	33.60	B	C
ATOM	3892	CD1	ILE	B	86	78.595	137.930	61.854	1.00	36.28	B	C
ATOM	3893	CD1	ILE	B	86	77.450	137.030	62.093	1.00	39.59	B	C
ATOM	3894	C	ILE	B	86	81.753	139.088	63.622	1.00	36.54	B	C
ATOM	3895	O	ILE	B	86	81.466	140.050	64.339	1.00	36.91	B	O
ATOM	3896	N	VAL	B	87	82.839	138.346	63.805	1.00	35.46	B	N
ATOM	3897	CA	VAL	B	87	83.763	138.638	64.891	1.00	36.32	B	C
ATOM	3898	CB	VAL	B	87	84.821	137.536	65.045	1.00	37.83	B	C
ATOM	3899	CG1	VAL	B	87	85.861	137.964	66.073	1.00	39.29	B	C
ATOM	3900	CG2	VAL	B	87	84.153	136.225	65.477	1.00	36.37	B	C
ATOM	3901	C	VAL	B	87	84.453	139.940	64.527	1.00	36.66	B	C

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ATOM	3902	O	VAL	B	87	84.677	140.813	65.373	1.00	37.75	B	O
ATOM	3903	N	ARG	B	88	84.753	140.082	63.243	1.00	35.47	B	N
ATOM	3904	CA	ARG	B	88	85.410	141.285	62.760	1.00	35.34	B	C
ATOM	3905	CB	ARG	B	88	85.711	141.134	61.271	1.00	36.76	B	C
ATOM	3906	CG	ARG	B	88	86.601	142.212	60.674	1.00	39.53	B	C
ATOM	3907	CD	ARG	B	88	85.966	142.785	59.414	1.00	40.93	B	C
ATOM	3908	NE	ARG	B	88	85.038	143.844	59.768	1.00	44.41	B	N
ATOM	3909	CZ	ARG	B	88	83.771	143.916	59.392	1.00	42.08	B	C
ATOM	3910	NH1	ARG	B	88	83.233	142.981	58.624	1.00	39.51	B	N
ATOM	3911	NH2	ARG	B	88	83.042	144.937	59.810	1.00	42.72	B	N
ATOM	3912	C	ARG	B	88	84.527	142.513	63.004	1.00	35.84	B	C
ATOM	3913	O	ARG	B	88	84.999	143.531	63.509	1.00	36.23	B	O
ATOM	3914	N	ALA	B	89	83.246	142.422	62.650	1.00	33.60	B	N
ATOM	3915	CA	ALA	B	89	82.342	143.549	62.852	1.00	33.77	B	C
ATOM	3916	CB	ALA	B	89	80.985	143.262	62.205	1.00	34.41	B	C
ATOM	3917	C	ALA	B	89	82.178	143.833	64.351	1.00	33.42	B	C
ATOM	3918	O	ALA	B	89	82.017	144.981	64.765	1.00	35.60	B	O
ATOM	3919	N	PHE	B	90	82.231	142.777	65.153	1.00	33.91	B	N
ATOM	3920	CA	PHE	B	90	82.113	142.879	66.604	1.00	33.04	B	C
ATOM	3921	CB	PHE	B	90	82.117	141.469	67.201	1.00	31.99	B	C
ATOM	3922	CG	PHE	B	90	82.091	141.433	68.707	1.00	32.81	B	C
ATOM	3923	CD1	PHE	B	90	80.918	141.692	69.407	1.00	31.25	B	C
ATOM	3924	CD2	PHE	B	90	83.238	141.098	69.422	1.00	31.99	B	C
ATOM	3925	CE1	PHE	B	90	80.892	141.612	70.804	1.00	31.58	B	C
ATOM	3926	CE2	PHE	B	90	83.220	141.014	70.814	1.00	32.00	B	C
ATOM	3927	CZ	PHE	B	90	82.051	141.268	71.507	1.00	28.24	B	C
ATOM	3928	C	PHE	B	90	83.289	143.695	67.155	1.00	33.50	B	C
ATOM	3929	O	PHE	B	90	83.094	144.635	67.927	1.00	32.15	B	O
ATOM	3930	N	VAL	B	91	84.503	143.333	66.738	1.00	35.16	B	N
ATOM	3931	CA	VAL	B	91	85.732	144.014	67.161	1.00	34.89	B	C
ATOM	3932	CB	VAL	B	91	86.980	143.238	66.667	1.00	34.31	B	C
ATOM	3933	CG1	VAL	B	91	88.256	143.998	67.019	1.00	32.33	B	C
ATOM	3934	CG2	VAL	B	91	87.009	141.846	67.285	1.00	33.66	B	C
ATOM	3935	C	VAL	B	91	85.832	145.454	66.629	1.00	37.76	B	C
ATOM	3936	O	VAL	B	91	86.092	146.407	67.369	1.00	37.82	B	O
ATOM	3937	N	GLU	B	92	85.630	145.590	65.327	1.00	38.23	B	N
ATOM	3938	CA	GLU	B	92	85.701	146.863	64.634	1.00	37.08	B	C
ATOM	3939	CB	GLU	B	92	85.494	146.583	63.142	1.00	41.38	B	C
ATOM	3940	CG	GLU	B	92	85.559	147.757	62.199	1.00	45.16	B	C
ATOM	3941	CD	GLU	B	92	85.818	147.295	60.761	1.00	48.44	B	C
ATOM	3942	OE1	GLU	B	92	85.402	148.000	59.821	1.00	50.05	B	O
ATOM	3943	OE2	GLU	B	92	86.452	146.229	60.575	1.00	48.03	B	O
ATOM	3944	C	GLU	B	92	84.687	147.876	65.156	1.00	36.14	B	C
ATOM	3945	O	GLU	B	92	84.934	149.082	65.162	1.00	33.34	B	O
ATOM	3946	N	ASN	B	93	83.533	147.400	65.599	1.00	36.05	B	N
ATOM	3947	CA	ASN	B	93	82.543	148.333	66.113	1.00	36.80	B	C
ATOM	3948	CB	ASN	B	93	81.169	147.973	65.582	1.00	35.11	B	C
ATOM	3949	CG	ASN	B	93	81.050	148.289	64.118	1.00	37.45	B	C
ATOM	3950	OD1	ASN	B	93	80.927	149.454	63.739	1.00	37.43	B	O
ATOM	3951	ND2	ASN	B	93	81.134	147.260	63.275	1.00	36.46	B	N
ATOM	3952	C	ASN	B	93	82.555	148.428	67.621	1.00	36.49	B	C
ATOM	3953	O	ASN	B	93	81.762	149.169	68.205	1.00	35.81	B	O
ATOM	3954	N	LYS	B	94	83.481	147.682	68.227	1.00	36.15	B	N
ATOM	3955	CA	LYS	B	94	83.678	147.659	69.672	1.00	37.92	B	C
ATOM	3956	CB	LYS	B	94	84.163	149.028	70.155	1.00	39.34	B	C
ATOM	3957	CG	LYS	B	94	85.491	149.471	69.565	1.00	40.70	B	C
ATOM	3958	CD	LYS	B	94	85.612	150.990	69.580	1.00	45.80	B	C
ATOM	3959	CE	LYS	B	94	87.008	151.453	69.164	1.00	47.75	B	C
ATOM	3960	NZ	LYS	B	94	87.427	150.903	67.841	1.00	49.75	B	N
ATOM	3961	C	LYS	B	94	82.408	147.283	70.406	1.00	39.29	B	C
ATOM	3962	O	LYS	B	94	82.132	147.815	71.478	1.00	40.90	B	O

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ATOM	3963	N	LEU	B	95	81.658	146.343	69.832	1.00	39.64	B	N
ATOM	3964	CA	LEU	B	95	80.406	145.875	70.408	1.00	36.49	B	C
ATOM	3965	CB	LEU	B	95	79.664	145.022	69.385	1.00	37.41	B	C
ATOM	3966	CG	LEU	B	95	79.480	145.754	68.054	1.00	36.92	B	C
ATOM	3967	CD1	LEU	B	95	78.678	144.892	67.088	1.00	38.88	B	C
ATOM	3968	CD2	LEU	B	95	78.771	147.055	68.301	1.00	36.33	B	C
ATOM	3969	C	LEU	B	95	80.601	145.094	71.698	1.00	36.28	B	C
ATOM	3970	O	LEU	B	95	79.634	144.591	72.285	1.00	33.04	B	O
ATOM	3971	N	TYR	B	96	81.854	144.977	72.129	1.00	34.16	B	N
ATOM	3972	CA	TYR	B	96	82.164	144.295	73.379	1.00	35.23	B	C
ATOM	3973	CB	TYR	B	96	83.531	143.606	73.297	1.00	35.13	B	C
ATOM	3974	CG	TYR	B	96	84.660	144.525	72.883	1.00	35.94	B	C
ATOM	3975	CD1	TYR	B	96	85.150	145.504	73.752	1.00	36.45	B	C
ATOM	3976	CE1	TYR	B	96	86.148	146.389	73.349	1.00	36.12	B	C
ATOM	3977	CD2	TYR	B	96	85.200	144.455	71.602	1.00	34.35	B	C
ATOM	3978	CE2	TYR	B	96	86.194	145.338	71.191	1.00	36.57	B	C
ATOM	3979	CZ	TYR	B	96	86.665	146.300	72.067	1.00	35.56	B	C
ATOM	3980	OH	TYR	B	96	87.648	147.173	71.656	1.00	37.89	B	O
ATOM	3981	C	TYR	B	96	82.190	145.346	74.485	1.00	37.49	B	C
ATOM	3982	O	TYR	B	96	82.151	145.019	75.674	1.00	38.58	B	O
ATOM	3983	N	GLY	B	97	82.235	146.610	74.070	1.00	38.85	B	N
ATOM	3984	CA	GLY	B	97	82.321	147.719	75.005	1.00	41.28	B	C
ATOM	3985	C	GLY	B	97	81.198	147.984	75.988	1.00	43.67	B	C
ATOM	3986	O	GLY	B	97	80.146	147.342	75.960	1.00	43.88	B	O
ATOM	3987	N	PRO	B	98	81.416	148.940	76.900	1.00	45.67	B	N
ATOM	3988	CD	PRO	B	98	82.662	149.715	77.061	1.00	45.53	B	C
ATOM	3989	CA	PRO	B	98	80.426	149.318	77.912	1.00	45.79	B	C
ATOM	3990	CB	PRO	B	98	81.118	150.446	78.667	1.00	45.43	B	C
ATOM	3991	CG	PRO	B	98	82.592	150.127	78.507	1.00	45.71	B	C
ATOM	3992	C	PRO	B	98	79.198	149.826	77.183	1.00	48.37	B	C
ATOM	3993	O	PRO	B	98	79.338	150.537	76.188	1.00	49.29	B	O
ATOM	3994	N	GLU	B	99	78.010	149.468	77.673	1.00	49.70	B	N
ATOM	3995	CA	GLU	B	99	76.739	149.895	77.077	1.00	51.70	B	C
ATOM	3996	CB	GLU	B	99	76.916	151.186	76.241	1.00	58.99	B	C
ATOM	3997	CG	GLU	B	99	75.608	151.848	75.739	1.00	66.78	B	C
ATOM	3998	CD	GLU	B	99	75.321	151.595	74.255	1.00	70.27	B	C
ATOM	3999	OE1	GLU	B	99	75.250	150.413	73.845	1.00	71.95	B	O
ATOM	4000	OE2	GLU	B	99	75.157	152.583	73.500	1.00	71.91	B	O
ATOM	4001	C	GLU	B	99	76.124	148.816	76.203	1.00	48.60	B	C
ATOM	4002	O	GLU	B	99	74.917	148.822	75.966	1.00	49.33	B	O
ATOM	4003	N	TYR	B	100	76.945	147.891	75.719	1.00	44.46	B	N
ATOM	4004	CA	TYR	B	100	76.432	146.827	74.870	1.00	41.82	B	C
ATOM	4005	CB	TYR	B	100	77.461	146.465	73.797	1.00	40.75	B	C
ATOM	4006	CG	TYR	B	100	77.656	147.580	72.793	1.00	39.52	B	C
ATOM	4007	CD1	TYR	B	100	78.698	148.493	72.926	1.00	37.95	B	C
ATOM	4008	CE1	TYR	B	100	78.845	149.561	72.037	1.00	40.38	B	C
ATOM	4009	CD2	TYR	B	100	76.757	147.753	71.739	1.00	40.75	B	C
ATOM	4010	CE2	TYR	B	100	76.893	148.820	70.835	1.00	42.33	B	C
ATOM	4011	CZ	TYR	B	100	77.941	149.719	70.991	1.00	41.90	B	C
ATOM	4012	OH	TYR	B	100	78.092	150.760	70.092	1.00	41.42	B	O
ATOM	4013	C	TYR	B	100	76.039	145.602	75.670	1.00	40.69	B	C
ATOM	4014	O	TYR	B	100	76.669	145.275	76.674	1.00	40.74	B	O
ATOM	4015	N	THR	B	101	74.979	144.936	75.230	1.00	38.66	B	N
ATOM	4016	CA	THR	B	101	74.493	143.749	75.912	1.00	39.87	B	C
ATOM	4017	CB	THR	B	101	73.289	143.104	75.156	1.00	42.67	B	C
ATOM	4018	OG1	THR	B	101	73.718	142.651	73.860	1.00	47.96	B	O
ATOM	4019	CG2	THR	B	101	72.167	144.119	74.965	1.00	42.55	B	C
ATOM	4020	C	THR	B	101	75.578	142.689	76.073	1.00	39.75	B	C
ATOM	4021	O	THR	B	101	76.418	142.489	75.195	1.00	39.88	B	O
ATOM	4022	N	LYS	B	102	75.555	142.033	77.225	1.00	39.27	B	N
ATOM	4023	CA	LYS	B	102	76.472	140.950	77.554	1.00	37.66	B	C

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ATOM	4024	CB	LYS	B	102	77.374	141.341	78.735	1.00	37.30	B	C
ATOM	4025	CG	LYS	B	102	78.184	142.631	78.590	1.00	36.96	B	C
ATOM	4026	CD	LYS	B	102	79.427	142.428	77.731	1.00	37.97	B	C
ATOM	4027	CE	LYS	B	102	80.342	143.645	77.748	1.00	31.85	B	C
ATOM	4028	NZ	LYS	B	102	79.735	144.825	77.080	1.00	32.33	B	N
ATOM	4029	C	LYS	B	102	75.525	139.827	78.004	1.00	37.23	B	C
ATOM	4030	O	LYS	B	102	74.759	140.015	78.939	1.00	40.29	B	O
ATOM	4031	N	PRO	B	103	75.515	138.675	77.314	1.00	36.05	B	N
ATOM	4032	CD	PRO	B	103	74.721	137.523	77.777	1.00	36.10	B	C
ATOM	4033	CA	PRO	B	103	76.307	138.316	76.134	1.00	35.43	B	C
ATOM	4034	CB	PRO	B	103	76.136	136.803	76.060	1.00	36.63	B	C
ATOM	4035	CG	PRO	B	103	74.756	136.593	76.589	1.00	35.24	B	C
ATOM	4036	C	PRO	B	103	75.727	139.030	74.905	1.00	34.93	B	C
ATOM	4037	O	PRO	B	103	74.532	139.324	74.857	1.00	32.94	B	O
ATOM	4038	N	TYR	B	104	76.575	139.334	73.932	1.00	33.48	B	N
ATOM	4039	CA	TYR	B	104	76.111	140.010	72.735	1.00	32.26	B	C
ATOM	4040	CB	TYR	B	104	77.255	140.811	72.103	1.00	31.07	B	C
ATOM	4041	CG	TYR	B	104	76.780	141.844	71.098	1.00	31.64	B	C
ATOM	4042	CD1	TYR	B	104	76.268	143.076	71.518	1.00	31.00	B	C
ATOM	4043	CE1	TYR	B	104	75.799	144.009	70.595	1.00	32.36	B	C
ATOM	4044	CD2	TYR	B	104	76.809	141.573	69.734	1.00	27.93	B	C
ATOM	4045	CE2	TYR	B	104	76.345	142.494	68.808	1.00	28.69	B	C
ATOM	4046	CZ	TYR	B	104	75.844	143.704	69.229	1.00	31.30	B	C
ATOM	4047	OH	TYR	B	104	75.410	144.616	68.284	1.00	29.26	B	O
ATOM	4048	C	TYR	B	104	75.601	138.933	71.780	1.00	32.76	B	C
ATOM	4049	O	TYR	B	104	76.380	138.202	71.170	1.00	34.35	B	O
ATOM	4050	N	LYS	B	105	74.283	138.841	71.661	1.00	33.99	B	N
ATOM	4051	CA	LYS	B	105	73.650	137.837	70.815	1.00	35.29	B	C
ATOM	4052	CB	LYS	B	105	72.362	137.361	71.474	1.00	37.61	B	C
ATOM	4053	CG	LYS	B	105	72.579	136.673	72.811	1.00	37.90	B	C
ATOM	4054	CD	LYS	B	105	71.256	136.196	73.387	1.00	41.87	B	C
ATOM	4055	CE	LYS	B	105	71.481	135.199	74.505	1.00	43.74	B	C
ATOM	4056	NZ	LYS	B	105	70.196	134.768	75.105	1.00	46.09	B	N
ATOM	4057	C	LYS	B	105	73.358	138.343	69.412	1.00	35.21	B	C
ATOM	4058	O	LYS	B	105	72.591	139.291	69.229	1.00	37.36	B	O
ATOM	4059	N	THR	B	106	73.962	137.693	68.423	1.00	33.47	B	N
ATOM	4060	CA	THR	B	106	73.791	138.093	67.040	1.00	35.77	B	C
ATOM	4061	CB	THR	B	106	75.042	138.803	66.496	1.00	37.38	B	C
ATOM	4062	OG1	THR	B	106	76.137	137.874	66.436	1.00	40.30	B	O
ATOM	4063	CG2	THR	B	106	75.419	139.933	67.380	1.00	35.86	B	C
ATOM	4064	C	THR	B	106	73.538	136.921	66.121	1.00	34.60	B	C
ATOM	4065	O	THR	B	106	74.034	135.825	66.334	1.00	36.86	B	O
ATOM	4066	N	TYR	B	107	72.768	137.162	65.076	1.00	35.66	B	N
ATOM	4067	CA	TYR	B	107	72.505	136.109	64.129	1.00	36.11	B	C
ATOM	4068	CB	TYR	B	107	71.117	135.524	64.361	1.00	32.19	B	C
ATOM	4069	CG	TYR	B	107	69.980	136.331	63.808	1.00	35.06	B	C
ATOM	4070	CD1	TYR	B	107	69.644	136.267	62.447	1.00	34.84	B	C
ATOM	4071	CE1	TYR	B	107	68.549	136.962	61.947	1.00	33.60	B	C
ATOM	4072	CD2	TYR	B	107	69.197	137.116	64.645	1.00	35.27	B	C
ATOM	4073	CE2	TYR	B	107	68.107	137.814	64.157	1.00	35.53	B	C
ATOM	4074	CZ	TYR	B	107	67.784	137.734	62.812	1.00	35.92	B	C
ATOM	4075	OH	TYR	B	107	66.696	138.432	62.349	1.00	37.70	B	O
ATOM	4076	C	TYR	B	107	72.644	136.687	62.733	1.00	37.34	B	C
ATOM	4077	O	TYR	B	107	72.453	137.878	62.527	1.00	36.74	B	O
ATOM	4078	N	TYR	B	108	73.011	135.839	61.784	1.00	39.17	B	N
ATOM	4079	CA	TYR	B	108	73.172	136.267	60.409	1.00	40.64	B	C
ATOM	4080	CB	TYR	B	108	74.646	136.311	60.014	1.00	39.81	B	C
ATOM	4081	CG	TYR	B	108	75.358	134.989	60.184	1.00	44.13	B	C
ATOM	4082	CD1	TYR	B	108	75.805	134.573	61.432	1.00	45.65	B	C
ATOM	4083	CE1	TYR	B	108	76.465	133.359	61.596	1.00	47.35	B	C
ATOM	4084	CD2	TYR	B	108	75.582	134.149	59.095	1.00	45.51	B	C

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ATOM	4085	CE2	TYR	B	108	76.235	132.932	59.246	1.00	46.72	B	C
ATOM	4086	CZ	TYR	B	108	76.678	132.542	60.500	1.00	48.50	B	C
ATOM	4087	OH	TYR	B	108	77.344	131.340	60.660	1.00	50.54	B	O
ATOM	4088	C	TYR	B	108	72.466	135.274	59.520	1.00	41.01	B	C
ATOM	4089	O	TYR	B	108	72.065	134.201	59.962	1.00	41.26	B	O
ATOM	4090	N	MET	B	109	72.314	135.653	58.264	1.00	40.28	B	N
ATOM	4091	CA	MET	B	109	71.683	134.821	57.254	1.00	41.39	B	C
ATOM	4092	CB	MET	B	109	70.163	134.906	57.291	1.00	39.60	B	C
ATOM	4093	CG	MET	B	109	69.493	134.372	58.520	1.00	45.08	B	C
ATOM	4094	SD	MET	B	109	67.671	134.367	58.330	1.00	51.80	B	S
ATOM	4095	CE	MET	B	109	67.453	135.541	57.009	1.00	46.71	B	C
ATOM	4096	C	MET	B	109	72.157	135.472	55.978	1.00	41.54	B	C
ATOM	4097	O	MET	B	109	71.960	136.671	55.793	1.00	44.10	B	O
ATOM	4098	N	GLY	B	110	72.795	134.702	55.109	1.00	41.10	B	N
ATOM	4099	CA	GLY	B	110	73.270	135.271	53.872	1.00	40.44	B	C
ATOM	4100	C	GLY	B	110	74.070	134.274	53.081	1.00	41.60	B	C
ATOM	4101	O	GLY	B	110	74.522	133.260	53.620	1.00	40.33	B	O
ATOM	4102	N	PRO	B	111	74.263	134.537	51.785	1.00	41.24	B	N
ATOM	4103	CD	PRO	B	111	73.878	135.761	51.062	1.00	39.91	B	C
ATOM	4104	CA	PRO	B	111	75.026	133.639	50.924	1.00	41.42	B	C
ATOM	4105	CB	PRO	B	111	74.869	134.277	49.551	1.00	42.40	B	C
ATOM	4106	CG	PRO	B	111	74.828	135.748	49.887	1.00	41.58	B	C
ATOM	4107	C	PRO	B	111	76.488	133.565	51.335	1.00	42.00	B	C
ATOM	4108	O	PRO	B	111	77.044	134.546	51.815	1.00	40.24	B	O
ATOM	4109	N	MET	B	112	77.089	132.391	51.146	1.00	44.25	B	N
ATOM	4110	CA	MET	B	112	78.506	132.163	51.426	1.00	46.44	B	C
ATOM	4111	CB	MET	B	112	78.696	131.216	52.613	1.00	46.95	B	C
ATOM	4112	CG	MET	B	112	78.142	131.736	53.945	1.00	49.46	B	C
ATOM	4113	SD	MET	B	112	78.820	133.328	54.521	1.00	49.32	B	S
ATOM	4114	CE	MET	B	112	77.529	133.824	55.652	1.00	51.34	B	C
ATOM	4115	C	MET	B	112	79.098	131.538	50.158	1.00	48.32	B	C
ATOM	4116	O	MET	B	112	78.384	130.908	49.371	1.00	46.69	B	O
ATOM	4117	N	PHE	B	113	80.400	131.712	49.964	1.00	49.99	B	N
ATOM	4118	CA	PHE	B	113	81.077	131.197	48.783	1.00	50.68	B	C
ATOM	4119	CB	PHE	B	113	81.546	132.381	47.942	1.00	50.00	B	C
ATOM	4120	CG	PHE	B	113	80.422	133.295	47.539	1.00	50.51	B	C
ATOM	4121	CD1	PHE	B	113	79.569	132.952	46.489	1.00	50.24	B	C
ATOM	4122	CD2	PHE	B	113	80.157	134.455	48.264	1.00	50.75	B	C
ATOM	4123	CE1	PHE	B	113	78.465	133.745	46.169	1.00	48.91	B	C
ATOM	4124	CE2	PHE	B	113	79.056	135.254	47.953	1.00	51.42	B	C
ATOM	4125	CZ	PHE	B	113	78.206	134.897	46.902	1.00	50.55	B	C
ATOM	4126	C	PHE	B	113	82.235	130.285	49.151	1.00	52.66	B	C
ATOM	4127	O	PHE	B	113	83.205	130.718	49.776	1.00	53.93	B	O
ATOM	4128	N	ARG	B	114	82.117	129.017	48.757	1.00	54.82	B	N
ATOM	4129	CA	ARG	B	114	83.123	128.000	49.055	1.00	57.13	B	C
ATOM	4130	CB	ARG	B	114	82.768	127.292	50.366	1.00	57.45	B	C
ATOM	4131	CG	ARG	B	114	82.788	128.146	51.615	1.00	59.39	B	C
ATOM	4132	CD	ARG	B	114	82.511	127.285	52.843	1.00	60.92	B	C
ATOM	4133	NE	ARG	B	114	81.118	126.853	52.900	1.00	64.84	B	N
ATOM	4134	CZ	ARG	B	114	80.236	127.287	53.800	1.00	67.07	B	C
ATOM	4135	NH1	ARG	B	114	80.602	128.163	54.730	1.00	66.16	B	N
ATOM	4136	NH2	ARG	B	114	78.980	126.860	53.761	1.00	67.88	B	N
ATOM	4137	C	ARG	B	114	83.269	126.910	47.982	1.00	58.76	B	C
ATOM	4138	O	ARG	B	114	82.357	126.673	47.192	1.00	57.57	B	O
ATOM	4139	N	TYR	B	115	84.432	126.255	47.977	1.00	60.63	B	N
ATOM	4140	CA	TYR	B	115	84.717	125.124	47.086	1.00	62.16	B	C
ATOM	4141	CB	TYR	B	115	86.154	125.179	46.555	1.00	60.71	B	C
ATOM	4142	CG	TYR	B	115	86.451	126.279	45.551	1.00	59.18	B	C
ATOM	4143	CD1	TYR	B	115	86.714	127.581	45.967	1.00	59.55	B	C
ATOM	4144	CE1	TYR	B	115	87.039	128.586	45.045	1.00	58.57	B	C
ATOM	4145	CD2	TYR	B	115	86.510	126.003	44.185	1.00	58.48	B	C

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ATOM	4146	CE2	TYR	B	115	86.831	126.996	43.252	1.00	57.18	B	C
ATOM	4147	CZ	TYR	B	115	87.099	128.285	43.687	1.00	59.33	B	C
ATOM	4148	OH	TYR	B	115	87.453	129.267	42.776	1.00	56.06	B	O
ATOM	4149	C	TYR	B	115	84.565	123.937	48.051	1.00	63.83	B	C
ATOM	4150	O	TYR	B	115	85.383	123.768	48.952	1.00	63.59	B	O
ATOM	4151	N	GLU	B	116	83.538	123.113	47.865	1.00	66.75	B	N
ATOM	4152	CA	GLU	B	116	83.277	122.022	48.805	1.00	69.76	B	C
ATOM	4153	CB	GLU	B	116	81.875	122.203	49.375	1.00	70.27	B	C
ATOM	4154	CG	GLU	B	116	81.728	123.448	50.201	1.00	70.75	B	C
ATOM	4155	CD	GLU	B	116	81.135	123.145	51.548	1.00	69.86	B	C
ATOM	4156	OE1	GLU	B	116	79.976	122.674	51.590	1.00	68.94	B	O
ATOM	4157	OE2	GLU	B	116	81.836	123.369	52.556	1.00	69.15	B	O
ATOM	4158	C	GLU	B	116	83.449	120.552	48.428	1.00	71.30	B	C
ATOM	4159	O	GLU	B	116	83.691	120.209	47.280	1.00	73.28	B	O
ATOM	4160	N	ARG	B	117	83.279	119.698	49.440	1.00	72.51	B	N
ATOM	4161	CA	ARG	B	117	83.409	118.242	49.344	1.00	73.43	B	C
ATOM	4162	CB	ARG	B	117	83.153	117.603	50.714	1.00	74.41	B	C
ATOM	4163	CG	ARG	B	117	83.663	116.172	50.861	1.00	76.17	B	C
ATOM	4164	CD	ARG	B	117	85.154	116.145	51.208	1.00	78.82	B	C
ATOM	4165	NE	ARG	B	117	85.992	116.733	50.163	1.00	80.85	B	N
ATOM	4166	CZ	ARG	B	117	87.306	116.924	50.274	1.00	83.10	B	C
ATOM	4167	NH1	ARG	B	117	87.935	116.579	51.390	1.00	83.68	B	N
ATOM	4168	NH2	ARG	B	117	87.996	117.454	49.266	1.00	83.59	B	N
ATOM	4169	C	ARG	B	117	82.511	117.558	48.313	1.00	73.82	B	C
ATOM	4170	O	ARG	B	117	82.749	116.403	47.954	1.00	75.41	B	O
ATOM	4171	N	PRO	B	118	81.432	118.223	47.873	1.00	72.43	B	N
ATOM	4172	CD	PRO	B	118	80.645	119.247	48.583	1.00	72.35	B	C
ATOM	4173	CA	PRO	B	118	80.605	117.539	46.872	1.00	71.28	B	C
ATOM	4174	CB	PRO	B	118	79.191	117.975	47.237	1.00	70.96	B	C
ATOM	4175	CG	PRO	B	118	79.406	119.366	47.716	1.00	72.27	B	C
ATOM	4176	C	PRO	B	118	81.008	117.950	45.451	1.00	69.82	B	C
ATOM	4177	O	PRO	B	118	80.753	117.221	44.492	1.00	70.50	B	O
ATOM	4178	N	GLN	B	119	81.637	119.119	45.325	1.00	68.33	B	N
ATOM	4179	CA	GLN	B	119	82.090	119.615	44.027	1.00	66.90	B	C
ATOM	4180	CB	GLN	B	119	80.908	120.181	43.226	1.00	69.63	B	C
ATOM	4181	CG	GLN	B	119	80.402	121.539	43.697	1.00	73.77	B	C
ATOM	4182	CD	GLN	B	119	79.882	121.516	45.119	1.00	75.30	B	C
ATOM	4183	OE1	GLN	B	119	78.824	120.947	45.391	1.00	76.63	B	O
ATOM	4184	NE2	GLN	B	119	80.627	122.130	46.036	1.00	75.70	B	N
ATOM	4185	C	GLN	B	119	83.189	120.677	44.150	1.00	64.45	B	C
ATOM	4186	O	GLN	B	119	83.051	121.793	43.646	1.00	63.04	B	O
ATOM	4187	N	ALA	B	120	84.289	120.323	44.811	1.00	62.42	B	N
ATOM	4188	CA	ALA	B	120	85.401	121.255	44.981	1.00	62.00	B	C
ATOM	4189	CB	ALA	B	120	86.503	120.617	45.807	1.00	61.33	B	C
ATOM	4190	C	ALA	B	120	85.930	121.634	43.608	1.00	62.06	B	C
ATOM	4191	O	ALA	B	120	85.593	121.007	42.612	1.00	63.64	B	O
ATOM	4192	N	GLY	B	121	86.770	122.649	43.540	1.00	61.87	B	N
ATOM	4193	CA	GLY	B	121	87.273	123.039	42.236	1.00	62.26	B	C
ATOM	4194	C	GLY	B	121	86.332	124.043	41.600	1.00	60.75	B	C
ATOM	4195	O	GLY	B	121	86.689	124.728	40.637	1.00	61.67	B	O
ATOM	4196	N	ARG	B	122	85.122	124.123	42.143	1.00	59.04	B	N
ATOM	4197	CA	ARG	B	122	84.123	125.068	41.661	1.00	59.02	B	C
ATOM	4198	CB	ARG	B	122	82.949	124.330	41.018	1.00	60.97	B	C
ATOM	4199	CG	ARG	B	122	81.708	125.187	40.831	1.00	61.68	B	C
ATOM	4200	CD	ARG	B	122	80.851	124.636	39.716	1.00	63.08	B	C
ATOM	4201	NE	ARG	B	122	81.507	124.811	38.425	1.00	66.42	B	N
ATOM	4202	CZ	ARG	B	122	81.112	124.223	37.300	1.00	67.58	B	C
ATOM	4203	NH1	ARG	B	122	80.056	123.415	37.307	1.00	68.35	B	N
ATOM	4204	NH2	ARG	B	122	81.771	124.440	36.168	1.00	66.20	B	N
ATOM	4205	C	ARG	B	122	83.609	125.929	42.806	1.00	56.50	B	C
ATOM	4206	O	ARG	B	122	83.271	125.418	43.874	1.00	56.04	B	O

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ATOM	4207	N	LEU B 123	83.561	127.237	42.587	1.00	55.75	B	N
ATOM	4208	CA	LEU B 123	83.067	128.144	43.616	1.00	55.48	B	C
ATOM	4209	CB	LEU B 123	83.512	129.575	43.336	1.00	55.53	B	C
ATOM	4210	CG	LEU B 123	83.056	130.570	44.405	1.00	57.18	B	C
ATOM	4211	CD1	LEU B 123	83.658	130.210	45.772	1.00	55.41	B	C
ATOM	4212	CD2	LEU B 123	83.468	131.959	43.975	1.00	55.86	B	C
ATOM	4213	C	LEU B 123	81.546	128.068	43.645	1.00	54.47	B	C
ATOM	4214	O	LEU B 123	80.870	128.469	42.701	1.00	55.11	B	O
ATOM	4215	N	ARG B 124	81.019	127.539	44.740	1.00	53.47	B	N
ATOM	4216	CA	ARG B 124	79.589	127.370	44.910	1.00	52.91	B	C
ATOM	4217	CB	ARG B 124	79.324	125.955	45.443	1.00	56.40	B	C
ATOM	4218	CG	ARG B 124	77.890	125.464	45.344	1.00	60.09	B	C
ATOM	4219	CD	ARG B 124	77.744	124.064	45.937	1.00	63.01	B	C
ATOM	4220	NE	ARG B 124	76.402	123.516	45.740	1.00	67.42	B	N
ATOM	4221	CZ	ARG B 124	75.970	122.365	46.257	1.00	68.53	B	C
ATOM	4222	NH1	ARG B 124	76.769	121.624	47.015	1.00	67.37	B	N
ATOM	4223	NH2	ARG B 124	74.732	121.949	46.008	1.00	69.49	B	N
ATOM	4224	C	ARG B 124	79.064	128.414	45.894	1.00	51.45	B	C
ATOM	4225	O	ARG B 124	79.760	128.793	46.840	1.00	49.09	B	O
ATOM	4226	N	GLN B 125	77.847	128.895	45.648	1.00	50.15	B	N
ATOM	4227	CA	GLN B 125	77.201	129.870	46.526	1.00	47.18	B	C
ATOM	4228	CB	GLN B 125	76.412	130.898	45.708	1.00	46.21	B	C
ATOM	4229	CG	GLN B 125	75.729	131.988	46.543	1.00	45.79	B	C
ATOM	4230	CD	GLN B 125	74.829	132.906	45.724	1.00	42.55	B	C
ATOM	4231	OE1	GLN B 125	75.198	133.360	44.643	1.00	43.43	B	O
ATOM	4232	NE2	GLN B 125	73.646	133.194	46.250	1.00	43.13	B	N
ATOM	4233	C	GLN B 125	76.240	129.116	47.447	1.00	47.12	B	C
ATOM	4234	O	GLN B 125	75.282	128.503	46.979	1.00	47.09	B	O
ATOM	4235	N	PHE B 126	76.514	129.146	48.750	1.00	47.83	B	N
ATOM	4236	CA	PHE B 126	75.662	128.486	49.744	1.00	48.88	B	C
ATOM	4237	CB	PHE B 126	76.477	127.615	50.713	1.00	53.72	B	C
ATOM	4238	CG	PHE B 126	77.342	126.595	50.041	1.00	60.25	B	C
ATOM	4239	CD1	PHE B 126	78.554	126.964	49.460	1.00	62.77	B	C
ATOM	4240	CD2	PHE B 126	76.944	125.257	49.981	1.00	63.78	B	C
ATOM	4241	CE1	PHE B 126	79.364	126.014	48.823	1.00	65.31	B	C
ATOM	4242	CE2	PHE B 126	77.743	124.296	49.349	1.00	66.15	B	C
ATOM	4243	CZ	PHE B 126	78.958	124.679	48.768	1.00	66.79	B	C
ATOM	4244	C	PHE B 126	74.959	129.552	50.567	1.00	45.70	B	C
ATOM	4245	O	PHE B 126	75.315	130.720	50.518	1.00	45.84	B	O
ATOM	4246	N	HIS B 127	73.962	129.146	51.333	1.00	43.74	B	N
ATOM	4247	CA	HIS B 127	73.256	130.092	52.168	1.00	43.76	B	C
ATOM	4248	CB	HIS B 127	71.835	130.312	51.649	1.00	43.13	B	C
ATOM	4249	CG	HIS B 127	71.787	130.900	50.272	1.00	45.63	B	C
ATOM	4250	CD2	HIS B 127	71.779	132.189	49.854	1.00	46.12	B	C
ATOM	4251	ND1	HIS B 127	71.784	130.129	49.128	1.00	46.73	B	N
ATOM	4252	CE1	HIS B 127	71.776	130.916	48.067	1.00	45.70	B	C
ATOM	4253	NE2	HIS B 127	71.773	132.170	48.480	1.00	46.39	B	N
ATOM	4254	C	HIS B 127	73.238	129.558	53.579	1.00	42.82	B	C
ATOM	4255	O	HIS B 127	72.743	128.458	53.829	1.00	43.58	B	O
ATOM	4256	N	GLN B 128	73.805	130.308	54.511	1.00	42.94	B	N
ATOM	4257	CA	GLN B 128	73.793	129.828	55.878	1.00	43.97	B	C
ATOM	4258	CB	GLN B 128	75.199	129.430	56.327	1.00	48.95	B	C
ATOM	4259	CG	GLN B 128	76.101	130.553	56.777	1.00	56.86	B	C
ATOM	4260	CD	GLN B 128	77.462	130.036	57.246	1.00	61.92	B	C
ATOM	4261	OE1	GLN B 128	78.324	130.809	57.678	1.00	63.94	B	O
ATOM	4262	NE2	GLN B 128	77.658	128.720	57.155	1.00	64.57	B	N
ATOM	4263	C	GLN B 128	73.168	130.758	56.897	1.00	42.39	B	C
ATOM	4264	O	GLN B 128	73.094	131.975	56.719	1.00	40.81	B	O
ATOM	4265	N	ILE B 129	72.677	130.143	57.959	1.00	41.94	B	N
ATOM	4266	CA	ILE B 129	72.067	130.850	59.070	1.00	39.97	B	C
ATOM	4267	CB	ILE B 129	70.685	130.268	59.415	1.00	38.28	B	C

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ATOM	4268	CG2	ILE	B	129	70.201	130.830	60.731	1.00	40.48	B	C
ATOM	4269	CG1	ILE	B	129	69.692	130.573	58.298	1.00	39.47	B	C
ATOM	4270	CD1	ILE	B	129	68.293	130.001	58.554	1.00	41.30	B	C
ATOM	4271	C	ILE	B	129	73.009	130.554	60.223	1.00	38.36	B	C
ATOM	4272	O	ILE	B	129	73.563	129.472	60.290	1.00	39.90	B	O
ATOM	4273	N	GLY	B	130	73.200	131.502	61.125	1.00	38.00	B	N
ATOM	4274	CA	GLY	B	130	74.076	131.235	62.245	1.00	39.32	B	C
ATOM	4275	C	GLY	B	130	73.932	132.243	63.364	1.00	39.16	B	C
ATOM	4276	O	GLY	B	130	73.350	133.308	63.183	1.00	39.85	B	O
ATOM	4277	N	VAL	B	131	74.450	131.894	64.533	1.00	39.51	B	N
ATOM	4278	CA	VAL	B	131	74.406	132.793	65.671	1.00	38.26	B	C
ATOM	4279	CB	VAL	B	131	73.333	132.378	66.718	1.00	38.66	B	C
ATOM	4280	CG1	VAL	B	131	71.971	132.239	66.048	1.00	35.70	B	C
ATOM	4281	CG2	VAL	B	131	73.735	131.099	67.403	1.00	34.34	B	C
ATOM	4282	C	VAL	B	131	75.767	132.768	66.333	1.00	38.51	B	C
ATOM	4283	O	VAL	B	131	76.544	131.822	66.168	1.00	36.89	B	O
ATOM	4284	N	GLU	B	132	76.052	133.834	67.061	1.00	37.79	B	N
ATOM	4285	CA	GLU	B	132	77.293	133.968	67.791	1.00	38.72	B	C
ATOM	4286	CB	GLU	B	132	78.348	134.705	66.947	1.00	40.05	B	C
ATOM	4287	CG	GLU	B	132	78.692	134.048	65.609	1.00	42.32	B	C
ATOM	4288	CD	GLU	B	132	79.397	132.698	65.748	1.00	45.94	B	C
ATOM	4289	OE1	GLU	B	132	79.779	132.117	64.712	1.00	47.38	B	O
ATOM	4290	OE2	GLU	B	132	79.574	132.209	66.882	1.00	48.94	B	O
ATOM	4291	C	GLU	B	132	76.911	134.810	69.001	1.00	38.37	B	C
ATOM	4292	O	GLU	B	132	76.259	135.847	68.861	1.00	39.92	B	O
ATOM	4293	N	ALA	B	133	77.265	134.342	70.188	1.00	37.42	B	N
ATOM	4294	CA	ALA	B	133	76.980	135.086	71.411	1.00	38.00	B	C
ATOM	4295	CB	ALA	B	133	76.099	134.280	72.340	1.00	34.58	B	C
ATOM	4296	C	ALA	B	133	78.331	135.354	72.051	1.00	35.45	B	C
ATOM	4297	O	ALA	B	133	79.053	134.422	72.388	1.00	35.06	B	O
ATOM	4298	N	PHE	B	134	78.657	136.630	72.214	1.00	36.66	B	N
ATOM	4299	CA	PHE	B	134	79.949	137.047	72.765	1.00	36.23	B	C
ATOM	4300	CB	PHE	B	134	80.573	138.127	71.881	1.00	35.84	B	C
ATOM	4301	CG	PHE	B	134	80.719	137.743	70.445	1.00	36.38	B	C
ATOM	4302	CD1	PHE	B	134	79.879	138.284	69.485	1.00	36.17	B	C
ATOM	4303	CD2	PHE	B	134	81.731	136.874	70.043	1.00	37.40	B	C
ATOM	4304	CE1	PHE	B	134	80.045	137.972	68.140	1.00	38.32	B	C
ATOM	4305	CE2	PHE	B	134	81.905	136.556	68.702	1.00	38.07	B	C
ATOM	4306	CZ	PHE	B	134	81.062	137.106	67.749	1.00	38.33	B	C
ATOM	4307	C	PHE	B	134	79.930	137.628	74.163	1.00	36.28	B	C
ATOM	4308	O	PHE	B	134	79.039	138.419	74.507	1.00	35.65	B	O
ATOM	4309	N	GLY	B	135	80.938	137.274	74.955	1.00	35.21	B	N
ATOM	4310	CA	GLY	B	135	81.048	137.854	76.279	1.00	35.36	B	C
ATOM	4311	C	GLY	B	135	80.775	136.991	77.486	1.00	38.85	B	C
ATOM	4312	O	GLY	B	135	81.176	137.357	78.590	1.00	38.46	B	O
ATOM	4313	N	SER	B	136	80.100	135.861	77.304	1.00	39.56	B	N
ATOM	4314	CA	SER	B	136	79.805	134.996	78.439	1.00	42.53	B	C
ATOM	4315	CB	SER	B	136	78.299	134.797	78.592	1.00	44.36	B	C
ATOM	4316	OG	SER	B	136	78.029	133.904	79.659	1.00	42.92	B	O
ATOM	4317	C	SER	B	136	80.443	133.628	78.324	1.00	44.25	B	C
ATOM	4318	O	SER	B	136	80.529	133.066	77.233	1.00	43.93	B	O
ATOM	4319	N	GLU	B	137	80.897	133.086	79.448	1.00	46.01	B	N
ATOM	4320	CA	GLU	B	137	81.473	131.754	79.409	1.00	47.82	B	C
ATOM	4321	CB	GLU	B	137	82.928	131.779	79.868	1.00	49.41	B	C
ATOM	4322	CG	GLU	B	137	83.205	132.273	81.252	1.00	50.50	B	C
ATOM	4323	CD	GLU	B	137	84.707	132.298	81.518	1.00	53.91	B	C
ATOM	4324	OE1	GLU	B	137	85.385	131.287	81.212	1.00	57.06	B	O
ATOM	4325	OE2	GLU	B	137	85.213	133.316	82.026	1.00	54.44	B	O
ATOM	4326	C	GLU	B	137	80.642	130.773	80.223	1.00	47.37	B	C
ATOM	4327	O	GLU	B	137	81.015	129.617	80.410	1.00	50.32	B	O
ATOM	4328	N	ASN	B	138	79.486	131.248	80.669	1.00	46.90	B	N

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ATOM	4329	CA	ASN	B	138	78.546	130.457	81.450	1.00	45.77	B	C
ATOM	4330	CB	ASN	B	138	77.376	131.348	81.858	1.00	46.47	B	C
ATOM	4331	CG	ASN	B	138	76.386	130.644	82.747	1.00	45.05	B	C
ATOM	4332	OD1	ASN	B	138	76.087	129.465	82.565	1.00	44.37	B	O
ATOM	4333	ND2	ASN	B	138	75.847	131.378	83.707	1.00	45.44	B	N
ATOM	4334	C	ASN	B	138	78.029	129.279	80.622	1.00	45.64	B	C
ATOM	4335	O	ASN	B	138	77.580	129.456	79.494	1.00	44.88	B	O
ATOM	4336	N	PRO	B	139	78.066	128.060	81.186	1.00	45.91	B	N
ATOM	4337	CD	PRO	B	139	78.467	127.755	82.569	1.00	45.12	B	C
ATOM	4338	CA	PRO	B	139	77.602	126.844	80.501	1.00	42.78	B	C
ATOM	4339	CB	PRO	B	139	77.898	125.736	81.511	1.00	42.81	B	C
ATOM	4340	CG	PRO	B	139	78.908	126.346	82.443	1.00	45.79	B	C
ATOM	4341	C	PRO	B	139	76.108	126.883	80.167	1.00	40.35	B	C
ATOM	4342	O	PRO	B	139	75.662	126.237	79.225	1.00	37.14	B	O
ATOM	4343	N	ALA	B	140	75.337	127.619	80.962	1.00	38.98	B	N
ATOM	4344	CA	ALA	B	140	73.894	127.705	80.742	1.00	39.93	B	C
ATOM	4345	CB	ALA	B	140	73.232	128.541	81.834	1.00	36.61	B	C
ATOM	4346	C	ALA	B	140	73.639	128.313	79.370	1.00	40.04	B	C
ATOM	4347	O	ALA	B	140	72.679	127.947	78.690	1.00	38.77	B	O
ATOM	4348	N	LEU	B	141	74.515	129.227	78.961	1.00	39.73	B	N
ATOM	4349	CA	LEU	B	141	74.386	129.847	77.660	1.00	39.37	B	C
ATOM	4350	CB	LEU	B	141	75.418	130.961	77.480	1.00	38.50	B	C
ATOM	4351	CG	LEU	B	141	75.336	131.749	76.165	1.00	39.97	B	C
ATOM	4352	CD1	LEU	B	141	73.923	132.321	75.999	1.00	37.96	B	C
ATOM	4353	CD2	LEU	B	141	76.380	132.865	76.158	1.00	36.10	B	C
ATOM	4354	C	LEU	B	141	74.594	128.771	76.602	1.00	40.29	B	C
ATOM	4355	O	LEU	B	141	73.842	128.694	75.623	1.00	40.13	B	O
ATOM	4356	N	ASP	B	142	75.600	127.926	76.795	1.00	39.55	B	N
ATOM	4357	CA	ASP	B	142	75.859	126.868	75.818	1.00	40.42	B	C
ATOM	4358	CB	ASP	B	142	76.910	125.869	76.314	1.00	41.28	B	C
ATOM	4359	CG	ASP	B	142	78.258	126.509	76.596	1.00	43.02	B	C
ATOM	4360	OD1	ASP	B	142	79.287	125.817	76.412	1.00	43.64	B	O
ATOM	4361	OD2	ASP	B	142	78.294	127.686	77.019	1.00	44.07	B	O
ATOM	4362	C	ASP	B	142	74.575	126.102	75.565	1.00	41.00	B	C
ATOM	4363	O	ASP	B	142	74.191	125.850	74.411	1.00	38.14	B	O
ATOM	4364	N	VAL	B	143	73.912	125.740	76.659	1.00	39.92	B	N
ATOM	4365	CA	VAL	B	143	72.685	124.964	76.578	1.00	40.95	B	C
ATOM	4366	CB	VAL	B	143	72.283	124.406	77.978	1.00	42.71	B	C
ATOM	4367	CG1	VAL	B	143	71.020	123.553	77.867	1.00	38.88	B	C
ATOM	4368	CG2	VAL	B	143	73.432	123.575	78.552	1.00	41.19	B	C
ATOM	4369	C	VAL	B	143	71.523	125.740	75.981	1.00	40.33	B	C
ATOM	4370	O	VAL	B	143	70.736	125.189	75.206	1.00	41.25	B	O
ATOM	4371	N	GLU	B	144	71.395	127.011	76.337	1.00	40.11	B	N
ATOM	4372	CA	GLU	B	144	70.298	127.786	75.782	1.00	39.68	B	C
ATOM	4373	CB	GLU	B	144	70.306	129.225	76.280	1.00	39.42	B	C
ATOM	4374	CG	GLU	B	144	69.056	129.986	75.826	1.00	39.61	B	C
ATOM	4375	CD	GLU	B	144	69.193	131.480	75.952	1.00	39.45	B	C
ATOM	4376	OE1	GLU	B	144	70.028	132.054	75.231	1.00	39.64	B	O
ATOM	4377	OE2	GLU	B	144	68.469	132.084	76.769	1.00	42.99	B	O
ATOM	4378	C	GLU	B	144	70.422	127.801	74.267	1.00	38.70	B	C
ATOM	4379	O	GLU	B	144	69.439	127.615	73.554	1.00	37.59	B	O
ATOM	4380	N	ILE	B	145	71.642	128.015	73.781	1.00	38.23	B	N
ATOM	4381	CA	ILE	B	145	71.888	128.068	72.349	1.00	36.42	B	C
ATOM	4382	CB	ILE	B	145	73.338	128.495	72.067	1.00	35.61	B	C
ATOM	4383	CG2	ILE	B	145	73.661	128.350	70.565	1.00	33.02	B	C
ATOM	4384	CG1	ILE	B	145	73.514	129.936	72.568	1.00	31.06	B	C
ATOM	4385	CD1	ILE	B	145	74.898	130.507	72.471	1.00	32.14	B	C
ATOM	4386	C	ILE	B	145	71.556	126.759	71.664	1.00	37.93	B	C
ATOM	4387	O	ILE	B	145	70.833	126.745	70.668	1.00	39.62	B	O
ATOM	4388	N	MET	B	146	72.056	125.653	72.197	1.00	39.93	B	N
ATOM	4389	CA	MET	B	146	71.752	124.362	71.596	1.00	41.07	B	C

FIGURE 11-82

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ATOM	4390	CB	MET	B	146	72.523	123.240	72.301	1.00	42.33	B	C
ATOM	4391	CG	MET	B	146	74.036	123.299	72.067	1.00	40.87	B	C
ATOM	4392	SD	MET	B	146	74.920	121.900	72.803	1.00	39.95	B	S
ATOM	4393	CE	MET	B	146	74.825	122.355	74.590	1.00	34.12	B	C
ATOM	4394	C	MET	B	146	70.247	124.114	71.664	1.00	39.87	B	C
ATOM	4395	O	MET	B	146	69.653	123.610	70.721	1.00	41.01	B	O
ATOM	4396	N	ALA	B	147	69.632	124.492	72.776	1.00	39.99	B	N
ATOM	4397	CA	ALA	B	147	68.193	124.327	72.936	1.00	41.47	B	C
ATOM	4398	CB	ALA	B	147	67.766	124.773	74.333	1.00	39.67	B	C
ATOM	4399	C	ALA	B	147	67.472	125.165	71.871	1.00	42.17	B	C
ATOM	4400	O	ALA	B	147	66.538	124.697	71.219	1.00	41.55	B	O
ATOM	4401	N	MET	B	148	67.907	126.407	71.703	1.00	42.45	B	N
ATOM	4402	CA	MET	B	148	67.312	127.284	70.707	1.00	42.94	B	C
ATOM	4403	CB	MET	B	148	67.997	128.647	70.741	1.00	46.14	B	C
ATOM	4404	CG	MET	B	148	67.479	129.658	69.713	1.00	43.30	B	C
ATOM	4405	SD	MET	B	148	68.395	131.188	69.870	1.00	43.36	B	S
ATOM	4406	CE	MET	B	148	69.933	130.725	69.072	1.00	37.12	B	C
ATOM	4407	C	MET	B	148	67.468	126.665	69.322	1.00	42.51	B	C
ATOM	4408	O	MET	B	148	66.558	126.731	68.498	1.00	41.44	B	O
ATOM	4409	N	ALA	B	149	68.620	126.052	69.077	1.00	42.32	B	N
ATOM	4410	CA	ALA	B	149	68.878	125.417	67.793	1.00	42.91	B	C
ATOM	4411	CB	ALA	B	149	70.296	124.905	67.744	1.00	41.35	B	C
ATOM	4412	C	ALA	B	149	67.900	124.271	67.530	1.00	44.19	B	C
ATOM	4413	O	ALA	B	149	67.455	124.073	66.395	1.00	43.13	B	O
ATOM	4414	N	LEU	B	150	67.571	123.510	68.572	1.00	44.32	B	N
ATOM	4415	CA	LEU	B	150	66.633	122.400	68.416	1.00	43.69	B	C
ATOM	4416	CB	LEU	B	150	66.734	121.449	69.612	1.00	43.38	B	C
ATOM	4417	CG	LEU	B	150	68.108	120.767	69.721	1.00	44.24	B	C
ATOM	4418	CD1	LEU	B	150	68.334	120.216	71.125	1.00	44.75	B	C
ATOM	4419	CD2	LEU	B	150	68.213	119.677	68.670	1.00	42.11	B	C
ATOM	4420	C	LEU	B	150	65.242	122.998	68.305	1.00	43.63	B	C
ATOM	4421	O	LEU	B	150	64.393	122.513	67.571	1.00	44.11	B	O
ATOM	4422	N	ASP	B	151	65.031	124.082	69.032	1.00	46.94	B	N
ATOM	4423	CA	ASP	B	151	63.765	124.795	69.021	1.00	48.07	B	C
ATOM	4424	CB	ASP	B	151	63.895	126.033	69.909	1.00	50.35	B	C
ATOM	4425	CG	ASP	B	151	62.562	126.615	70.312	1.00	54.98	B	C
ATOM	4426	OD1	ASP	B	151	61.662	126.685	69.444	1.00	57.28	B	O
ATOM	4427	OD2	ASP	B	151	62.421	127.021	71.497	1.00	55.33	B	O
ATOM	4428	C	ASP	B	151	63.500	125.196	67.559	1.00	49.08	B	C
ATOM	4429	O	ASP	B	151	62.379	125.086	67.052	1.00	49.36	B	O
ATOM	4430	N	PHE	B	152	64.548	125.643	66.877	1.00	47.65	B	N
ATOM	4431	CA	PHE	B	152	64.418	126.059	65.487	1.00	47.00	B	C
ATOM	4432	CB	PHE	B	152	65.766	126.558	64.960	1.00	45.53	B	C
ATOM	4433	CG	PHE	B	152	65.781	126.821	63.488	1.00	42.49	B	C
ATOM	4434	CD1	PHE	B	152	65.073	127.889	62.947	1.00	44.52	B	C
ATOM	4435	CD2	PHE	B	152	66.527	126.017	62.640	1.00	41.32	B	C
ATOM	4436	CE1	PHE	B	152	65.113	128.154	61.574	1.00	41.31	B	C
ATOM	4437	CE2	PHE	B	152	66.573	126.273	61.272	1.00	42.37	B	C
ATOM	4438	CZ	PHE	B	152	65.865	127.344	60.740	1.00	40.65	B	C
ATOM	4439	C	PHE	B	152	63.914	124.929	64.601	1.00	46.69	B	C
ATOM	4440	O	PHE	B	152	62.968	125.103	63.828	1.00	45.22	B	O
ATOM	4441	N	PHE	B	153	64.548	123.770	64.709	1.00	45.66	B	N
ATOM	4442	CA	PHE	B	153	64.155	122.634	63.889	1.00	47.78	B	C
ATOM	4443	CB	PHE	B	153	65.181	121.514	64.028	1.00	45.21	B	C
ATOM	4444	CG	PHE	B	153	66.482	121.814	63.349	1.00	41.98	B	C
ATOM	4445	CD1	PHE	B	153	67.630	122.074	64.090	1.00	42.49	B	C
ATOM	4446	CD2	PHE	B	153	66.557	121.852	61.965	1.00	39.43	B	C
ATOM	4447	CE1	PHE	B	153	68.834	122.369	63.460	1.00	39.03	B	C
ATOM	4448	CE2	PHE	B	153	67.751	122.145	61.327	1.00	39.64	B	C
ATOM	4449	CZ	PHE	B	153	68.895	122.405	62.077	1.00	40.42	B	C
ATOM	4450	C	PHE	B	153	62.748	122.132	64.203	1.00	49.38	B	C

FIGURE 11-83

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ATOM	4451	O	PHE	B	153	61.968	121.866	63.288	1.00	49.63	B	O
ATOM	4452	N	LYS	B	154	62.418	122.005	65.485	1.00	50.86	B	N
ATOM	4453	CA	LYS	B	154	61.085	121.566	65.859	1.00	53.62	B	C
ATOM	4454	CB	LYS	B	154	60.859	121.712	67.371	1.00	55.44	B	C
ATOM	4455	CG	LYS	B	154	59.498	121.182	67.846	1.00	59.32	B	C
ATOM	4456	CD	LYS	B	154	59.198	121.492	69.315	1.00	62.34	B	C
ATOM	4457	CE	LYS	B	154	60.184	120.802	70.261	1.00	67.24	B	C
ATOM	4458	NZ	LYS	B	154	59.887	121.086	71.703	1.00	68.33	B	N
ATOM	4459	C	LYS	B	154	60.134	122.492	65.109	1.00	55.31	B	C
ATOM	4460	O	LYS	B	154	59.169	122.048	64.491	1.00	56.22	B	O
ATOM	4461	N	GLN	B	155	60.437	123.786	65.151	1.00	56.55	B	N
ATOM	4462	CA	GLN	B	155	59.619	124.794	64.489	1.00	57.26	B	C
ATOM	4463	CB	GLN	B	155	60.168	126.189	64.785	1.00	59.84	B	C
ATOM	4464	CG	GLN	B	155	59.136	127.308	64.741	1.00	64.85	B	C
ATOM	4465	CD	GLN	B	155	58.225	127.302	65.960	1.00	69.34	B	C
ATOM	4466	OE1	GLN	B	155	58.698	127.282	67.104	1.00	70.61	B	O
ATOM	4467	NE2	GLN	B	155	56.912	127.327	65.723	1.00	68.92	B	N
ATOM	4468	C	GLN	B	155	59.554	124.576	62.973	1.00	56.54	B	C
ATOM	4469	O	GLN	B	155	58.585	124.974	62.332	1.00	57.71	B	O
ATOM	4470	N	LEU	B	156	60.576	123.953	62.393	1.00	55.03	B	N
ATOM	4471	CA	LEU	B	156	60.562	123.693	60.953	1.00	55.34	B	C
ATOM	4472	CB	LEU	B	156	61.976	123.503	60.405	1.00	52.89	B	C
ATOM	4473	CG	LEU	B	156	62.890	124.716	60.337	1.00	52.06	B	C
ATOM	4474	CD1	LEU	B	156	64.156	124.314	59.617	1.00	52.30	B	C
ATOM	4475	CD2	LEU	B	156	62.211	125.850	59.602	1.00	51.97	B	C
ATOM	4476	C	LEU	B	156	59.756	122.440	60.634	1.00	56.34	B	C
ATOM	4477	O	LEU	B	156	59.392	122.202	59.481	1.00	56.00	B	O
ATOM	4478	N	GLY	B	157	59.484	121.638	61.658	1.00	56.55	B	N
ATOM	4479	CA	GLY	B	157	58.737	120.415	61.445	1.00	57.77	B	C
ATOM	4480	C	GLY	B	157	59.678	119.245	61.240	1.00	58.44	B	C
ATOM	4481	O	GLY	B	157	59.250	118.157	60.857	1.00	59.37	B	O
ATOM	4482	N	ILE	B	158	60.966	119.486	61.479	1.00	58.39	B	N
ATOM	4483	CA	ILE	B	158	62.012	118.471	61.363	1.00	57.73	B	C
ATOM	4484	CB	ILE	B	158	63.385	119.133	61.122	1.00	55.92	B	C
ATOM	4485	CG2	ILE	B	158	64.489	118.114	61.228	1.00	55.95	B	C
ATOM	4486	CG1	ILE	B	158	63.397	119.806	59.750	1.00	56.48	B	C
ATOM	4487	CD1	ILE	B	158	64.641	120.619	59.468	1.00	54.51	B	C
ATOM	4488	C	ILE	B	158	62.020	117.754	62.711	1.00	59.69	B	C
ATOM	4489	O	ILE	B	158	62.290	118.374	63.741	1.00	58.98	B	O
ATOM	4490	N	GLN	B	159	61.734	116.452	62.710	1.00	61.48	B	N
ATOM	4491	CA	GLN	B	159	61.664	115.705	63.963	1.00	61.73	B	C
ATOM	4492	CB	GLN	B	159	60.268	115.103	64.095	1.00	62.40	B	C
ATOM	4493	CG	GLN	B	159	59.169	116.130	63.941	1.00	64.55	B	C
ATOM	4494	CD	GLN	B	159	57.792	115.510	63.827	1.00	67.02	B	C
ATOM	4495	OE1	GLN	B	159	57.339	114.805	64.730	1.00	66.97	B	O
ATOM	4496	NE2	GLN	B	159	57.113	115.775	62.714	1.00	66.77	B	N
ATOM	4497	C	GLN	B	159	62.707	114.617	64.190	1.00	61.57	B	C
ATOM	4498	O	GLN	B	159	63.030	114.298	65.337	1.00	62.32	B	O
ATOM	4499	N	GLN	B	160	63.238	114.057	63.107	1.00	61.48	B	N
ATOM	4500	CA	GLN	B	160	64.219	112.975	63.194	1.00	59.73	B	C
ATOM	4501	CB	GLN	B	160	64.116	112.085	61.950	1.00	61.26	B	C
ATOM	4502	CG	GLN	B	160	62.693	111.879	61.438	1.00	63.33	B	C
ATOM	4503	CD	GLN	B	160	62.631	110.978	60.211	1.00	65.66	B	C
ATOM	4504	OE1	GLN	B	160	61.660	111.012	59.447	1.00	66.63	B	O
ATOM	4505	NE2	GLN	B	160	63.663	110.158	60.022	1.00	64.98	B	N
ATOM	4506	C	GLN	B	160	65.642	113.497	63.323	1.00	58.23	B	C
ATOM	4507	O	GLN	B	160	66.441	113.394	62.386	1.00	57.34	B	O
ATOM	4508	N	ILE	B	161	65.969	114.038	64.491	1.00	57.10	B	N
ATOM	4509	CA	ILE	B	161	67.303	114.594	64.709	1.00	55.89	B	C
ATOM	4510	CB	ILE	B	161	67.296	116.143	64.553	1.00	54.60	B	C
ATOM	4511	CG2	ILE	B	161	66.911	116.527	63.130	1.00	50.45	B	C

FIGURE 11-84

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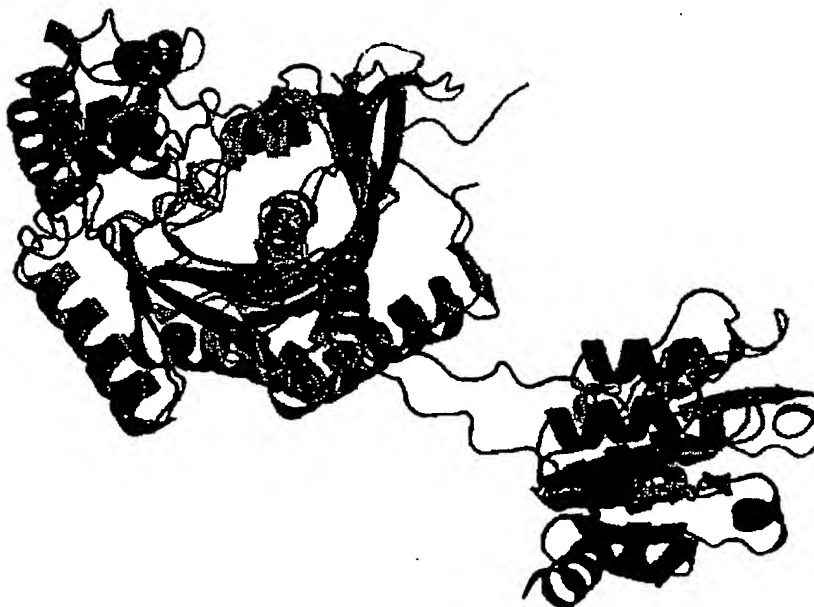
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[Continued on next page]

(54) Title: PURIFIED POLYPEPTIDES FROM ENTEROCOCCUS FAECALIS



(57) Abstract: The present invention relates to novel drug targets for pathogenic bacteria. Accordingly, the invention provides purified protein comprising the amino acid sequence set forth in SEQ ID NO: 4. The invention also provides biochemical and biophysical characteristics of the polypeptides of the invention.

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International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 50555 A (HUMAN GENOME SCIENCES INC ;BARASH STEVEN C (US); DILLON PATRICK J) 12 November 1998 (1998-11-12) SeqIdNo 5 abstract; claims; figure 1 page 2, line 33 -page 5, line 24 page 33, line 3 - line 4 page 57, line 14 - line 25 page 104</p> <p style="text-align: center;">--- -/--</p>	<p>1-32,36, 37,40, 64-69</p>

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 70955 A (YAMAMOTO ROBERT T ;OHLSEN KARI L (US); WALL DANIEL (US); XU H HOWA) 27 September 2001 (2001-09-27) SeqIdNos 6780,10877 abstract; claims page 7, line 13 - line 15 page 7, line 30 page 9, line 3 - line 5 page 9, line 16 page 261	1-32,36, 37,40, 64-69
L	-& DATABASE GSN [Online] EMBL; 13 February 2002 (2002-02-13) HASELBECK ET AL.: "Enterococcus faecalis DNA for cellular proliferation protein #571" retrieved from EBI Database accession no. AAS53143 XP002268058 SeqIdNo 6780 of W00170955 the whole document	
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P,X	---	
	WO 02 77183 A (ELITRA PHARM. INC.) 3 October 2002 (2002-10-03) SeqIdNos 6394, 42578 abstract; claims	1-32,36, 37,40, 64-69
L	-& DATABASE GSN [Online] EMBL; 19 June 2003 (2003-06-19) WANG ET AL.: "Prokaryotic essential gene #181" retrieved from EBI Database accession no. ACA18524 XP002268060 SeqIdNo 6394 of W00277183 the whole document	
L	-& DATABASE GSP [Online] EMBL; 19 June 2003 (2003-06-19) WANG ET AL.: "Protein encoded by prokaryotic essential gene #181" retrieved from EBI Database accession no. ABU14654 XP002268061 SeqIdNo 42578 of W00277183 the whole document	

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INTERNATIONAL SEARCH REPORT

International Application No

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>DATABASE EM PRO [Online] EMBL; 29 March 2003 (2003-03-29) PAULSEN ET AL.: "Enterococcus faecalis V583, section 7 of 11 of the complete genome" retrieved from EBI Database accession no. AE016953 XP002268062 the whole document -& PAULSEN ET AL.: "Role of mobile DNA in the evolution of vancomycin-resistant Enterococcus faecalis" SCIENCE, vol. 299, 28 March 2003 (2003-03-28), pages 2071-2074, XP002268057 ---</p>	1,13,26, 27
A	<p>ARNEZ J G ET AL: "CRYSTAL STRUCTURE OF HISTIDYL-TRNA SYNTHETASE FROM ESCHERICHIA COLI COMPLEXED WITH HISTIDYL-ADENYLATE" EMBO JOURNAL, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 14, no. 17, 1995, pages 4143-4155, XP002028684 ISSN: 0261-4189 the whole document ---</p>	1-41, 55-69
A	<p>YAREMCHUK A ET AL: "A succession of substrate induced conformational changes ensures the amino acid specificity of Thermus thermophilus prolyl-tRNA synthetase: comparison with histidyl-tRNA synthetase" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 309, no. 4, 15 June 2001 (2001-06-15), pages 989-1002, XP004469242 ISSN: 0022-2836 ---</p>	
A	<p>WO 01 09154 A (UNIV YALE ;SILVIAN LAURA F (US); STEITZ THOMAS A (US); WANG JIMIN) 8 February 2001 (2001-02-08) ---</p>	
A	<p>US 6 197 495 B1 (RICHARDSON CHRISTINE MARY ET AL) 6 March 2001 (2001-03-06) -----</p>	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/01135

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 42-54, 71-74
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(v) PCT - Presentation of information
2. ☒ Claims Nos.: 70
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 70

Present claim 70 relate to a compound defined by reference to a desirable characteristic or property, namely having been identified during a computer-assisted process.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 03/01135

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9850555	A	12-11-1998	AU 735444 B2	05-07-2001
			AU 7279398 A	27-11-1998
			AU 745787 B2	28-03-2002
			AU 7280598 A	27-11-1998
			CN 1268178 T	27-09-2000
			CN 1261916 T	02-08-2000
			EP 1002090 A2	24-05-2000
			EP 0981625 A2	01-03-2000
			JP 2002516571 T	04-06-2002
			JP 2002529046 T	03-09-2002
			US 2002045737 A1	18-04-2002
			WO 9850554 A2	12-11-1998
			WO 9850555 A2	12-11-1998
			US 2003017495 A1	23-01-2003
WO 0170955	A	27-09-2001	AU 4934501 A	03-10-2001
			CA 2404260 A1	27-09-2001
			EP 1268774 A2	02-01-2003
			WO 0170955 A2	27-09-2001
			US 2002061569 A1	23-05-2002
WO 0277183	A	03-10-2002	US 2002061569 A1	23-05-2002
			WO 02077183 A2	03-10-2002
WO 0109154	A	08-02-2001	AU 6391500 A	19-02-2001
			CA 2380335 A1	08-02-2001
			EP 1200564 A2	02-05-2002
			WO 0109154 A2	08-02-2001
			US 6631329 B1	07-10-2003
US 6197495	B1	06-03-2001	US 6037117 A	14-03-2000